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(54) Title: RETINOID ANTAGONISTS AND USES THEREOF			
(57) Abstract			
<p>Retinoid antagonist compounds have been found to be useful in the prevention and/or minimization of surgical adhesion formation. Also provided by the invention are certain novel substituted (5,6)-dihydronaphthalenyl compounds which are retinoid antagonists and possess the above-mentioned property in addition to their use as antiinflammatory agents for chronic skin inflammatory diseases, as agents for the treatment of rheumatic diseases and as agents for the treatment of various tumors as well as non-malignant proliferative skin conditions.</p>			

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RETINOID ANTAGONISTS AND USES THEREOF

FIELD OF THE INVENTION

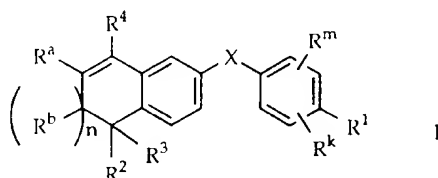
10 The present invention is directed to methods for the minimization
or prevention of post-surgical adhesion formation using retinoid
antagonist compounds, particularly the retinoid antagonist compounds
disclosed in U.S. Patent 5,618,839; see also EP 661,259 A1 published July 5,
1995. The above-mentioned U.S. patent is herein incorporated by
15 reference in its entirety.

 In another aspect the present invention provides a novel series of
substituted (5,6)-dihydronaphthalenyl compounds which are also potent
retinoid antagonists. These compounds are useful as antiinflammatory
20 agents for chronic skin inflammatory diseases such as psoriasis and atopic
dermatitis, as agents for the treatment of rheumatic diseases such as
rheumatoid arthritis, as antitumor agents for the treatment of various
tumors as well as non-malignant proliferative skin conditions and as
agents for the minimization or prevention of post-surgical adhesion
25 formation.

BACKGROUND OF THE INVENTION

Retinoic acid and its natural and synthetic analogs exert a wide array of biological effects. They have been shown to affect cellular growth and differentiation and are promising drugs for the treatment of several cancers.

U.S. Patent 5,618,839 and EP 661,259 A1 published July 5, 1995 disclose a series of substituted (5,6)-dihydronaphthalenyl compounds of the formula




or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable esters or solvates thereof, in which

X is

- O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-,
- COS-, -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
- COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
- NHCH₂- or -CR⁵=CR⁶-;

-3-

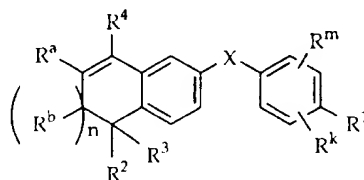
- 5 R^m and R^k are independently hydrogen, halogen, C_{1-6} alkyl, hydroxy, C_{1-6} -alkyloxy or nitro;
- n is zero or one;
- R^4 is $-(CH_2)_t-Y$, C_{1-6} alkyl, or C_{3-6} cycloalkyl;
- R^1 is $-CO_2Z$, C_{1-6} alkyl, CH_2OH , $-CONHR^y$, or CHO ;
- 10 R^2 and R^3 are independently hydrogen or C_{1-6} alkyl;
- R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula
- 
- 15 Y is naphthyl or phenyl, both radicals can be optionally substituted with one to three same or different C_{1-6} alkyl or halogen;
- Z is hydrogen or C_{1-6} alkyl;
- R^5 , R^6 and R^y are independently hydrogen or C_{1-6} alkyl; and
- 20 t is zero to six.

These compounds are reported to have retinoid-like activity and to be useful for preventing and/or treating various skin disorders such as acne, psoriasis and damage from irradiation, for treatment of various

25 tumors and non-malignant proliferative skin diseases and for treatment of rheumatic diseases such as rheumatoid arthritis.

5 The present inventors have discovered that certain compounds included within the scope of EP 661,259A1 and U.S. Patent 5,618,839 are retinoid antagonists, i.e., they bind to all three RAR retinoic acid receptor subtypes (α , β and γ) but do not activate at least two of the three subtypes when tested in a standard transactivation assay. These retinoid antagonist

10 compounds have the general formula



IA

or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable

15 esters or solvates thereof, in which

X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
 20 -NHCH₂- or -CR⁵ = CR⁶-;

R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆alkyloxy or nitro;

n is zero or one;

R⁴ is -(CH₂)_t-Y;

5 R¹ is -CO₂Z, -C₁₋₆ alkyl, CH₂OH, -CONHR^y or CHO;
R² and R³ are independently hydrogen or C₁₋₆ alkyl;
R^a and R^b are independently hydrogen or C₁₋₆ alkyl; but when n is
one, R^a and R^b together can form a radical of the
formula



10

Y is phenyl or naphthyl and both radicals can be optionally substituted with one to three same or different C₁₋₆ alkyl or halogen groups;

Z is hydrogen or C₁₋₆ alkyl;

15 R⁵, R⁶ and R^y are independently hydrogen or C₁₋₆ alkyl; and

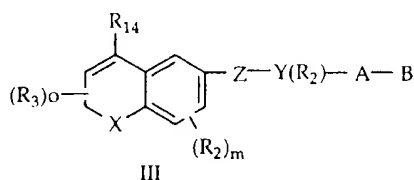
t is zero to six.

U.S. Patent 5,534,261 discloses that retinoids, particularly all-trans retinoic acid, can be used to minimize or prevent adhesion formation following surgery. There is no illustration or suggestion, however, that a retinoid antagonist compound would have this same utility.

Published patent application WO 97/09297 discloses retinoid antagonist compounds of the general formula

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-6-



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wherein X is S, O or NR¹ where R¹ is H or alkyl of 1-6 carbons, or X is [C(R₁)₂]_n where R₁ is independently H or alkyl of 1 to 6 carbons, and n is 0, 1 or 2;

10 R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

15

m is 0, 1, 2 or 3;

o is 0, 1, 2 or 3;

20

Z is -C≡C-,

-N=N-,

-N=CR₁-,

-CR₁=N,

-(CR₁=CR₁)_n where n' is 0 or an integer of 1-5,

25

-CO-NR₁-,

-7-

- 5 -CS-NR₁-,
 -NR₁-CO,
 -NR₁-CS,
 -COO-,
 -OCO-,
 10 -CSO-, or
 -OCS-;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 15 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups, or

when Z is -(CR₁=CR₁)_{n'} and n' is 3, 4 or 5, then Y represents a direct valence bond between said (CR₁=CR₁)_{n'} group and B;

20 A is (CH₂)_q where q is 0 or an integer of 1-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, or alkynyl having 2-6 carbons and 1 or 2 triple bonds;

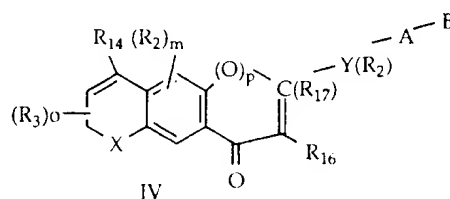
25 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, -CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O,

- 5 -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group having 1-5 carbons, R₈ is an alkyl group of 1 to 10 carbons, or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is a divalent alkyl radical of 2-5 carbons; and
- R₁₄ is (R₁₅)_r-phenyl, (R₁₅)_r-naphthyl or (R₁₅)_r-heteroaryl where the
- 15 heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is 0 or an integer of 1-5; and R₁₅ is independently H, F, Cl, Br, I, NO₂, N(R₈)₂, N(R₈)COR₈, NR₈(CON(R₈)₂, OH, OCOR₈, OR₈, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 2 to 10
- 20 carbons and 1 to 3 double bonds, alkynyl group having 2-10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons.

Also disclosed in this publication as retinoid antagonist compounds

25 are compounds of the general formula

-9-



5

wherein X is S, O or NR¹ where R¹ is H or alkyl of 1-6 carbons, or

X is [C(R₁)₂]_n, where R₁ is independently H or alkyl of 1 to 6 carbons,

10

and n is an integer between 0 and 2;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

15

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

20

o is an integer having the value of 0 - 3;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolizyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups;

25

5

A is $(\text{CH}_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

10

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR_8 , $\text{CONR}_9\text{R}_{10}$, $-\text{CH}_2\text{OH}$, $\text{CH}_2\text{OR}_{11}$, $\text{CH}_2\text{OCOR}_{11}$, CHO, $\text{CH}(\text{OR}_{12})_2$, CHOR_{13}O , $-\text{COR}_7$, $\text{CR}_7(\text{OR}_{12})_2$, $\text{CR}_7\text{OR}_{13}\text{O}$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, and

20

25

R_{14} is $(\text{R}_{15})_r$ -phenyl, $(\text{R}_{15})_r$ -naphthyl, or $(\text{R}_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0-5, and

- 5 R_{15} is independently H, F, Cl, Br, I, NO_2 , $\text{N}(\text{R}_8)_2$, $\text{N}(\text{R}_8)\text{COR}_8$,
 $\text{NR}_8\text{CON}(\text{R}_8)_2$, OH, OCOR_8 , OR_8 , CN, an alkyl group having 1 to 10
carbons, fluoro substituted alkyl group having 1 to 10 carbons, an
alkenyl group having 1 to 10 carbons and 1 to 3 double bonds,
alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a
10 trialkylsilyl or trialkylsilyloxy group where the alkyl groups
independently have 1 to 6 carbons;

R_{16} is H, lower alkyl of 1 to 6 carbons;

- 15 R_{17} is H, lower alkyl of 1 to 6 carbons, OH or OCOR_{11} , and

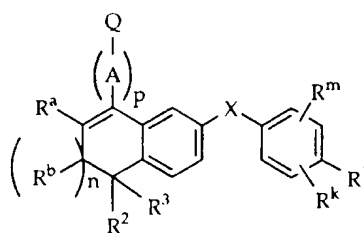
p is zero or 1, with the proviso that when p is 1 then there is no R_{17}
substituent group, and m is an integer between 0 and 2.

- 20 The above-mentioned retinoid antagonist compounds are said to be
useful for preventing certain undesired side effects of retinoids which are
administered for the treatment or prevention of certain diseases or
conditions. They are also said to be useful in the treatment of acute or
chronic toxicity resulting from overdose or poisoning by retinoid drugs or
25 Vitamin A.

The present inventors have surprisingly found that retinoid
antagonist compounds, particularly the retinoid antagonists disclosed

5 above which are generically taught in EP 661,259 A1 and in U.S. Patent 5,618,839, have utility in preventing or minimizing post-surgical adhesion formation and, in fact, are significantly more active for this use than the retinoid agonists described in U.S. Patent 5,534,261.

10 In another aspect, the present inventors have prepared a novel series of substituted (5,6)-dihydronaphthalenyl compounds which also are potent retinoid antagonists. These new compounds display the utilities of the retinoid antagonist compounds described in U.S. Patent 5,618,839 and EP 661,259 A1, and also possess the ability to prevent or minimize post-
 15 surgical adhesion formation. This new series of retinoid antagonists is generically defined by the formula



II

20 or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable esters or solvates thereof, in which

X is $-O-CO-$, $-NH-CO-$, $-CS-NH-$, $-CO-O-$, $-CO-NH-$, $-COS-$,
 $-SCO-$, $-SCH_2-$, $-CH_2-CH_2-$, $-C\equiv C-$, $-CH_2-NH-$,

5 $-\text{COCH}_2-$, $-\text{NHCS}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{O}-$, $-\text{OCH}_2-$,
 $-\text{NHCH}_2-$ or $-\text{CR}^5 = \text{CR}^6-$;

R^m and R^k are independently hydrogen, halogen, C_{1-6} alkyl, hydroxy,
 C_{1-6} alkyloxy or nitro;

n is zero or one;

10 A is $-\text{NH}(\text{CH}_2)_m-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{O}-$, $-\text{C}\equiv\text{C}-$, $-\text{CR}^8\text{R}^9$,
 $-\text{CR}^8 = \text{CR}^9-$, phenyl, phenyl substituted by a C_{1-6} alkyl,
 C_{1-6} alkoxy, halogen, CO_2R^8 , $-(\text{CH}_2)_m\text{OR}^8$,
 $-(\text{CH}_2)_m\text{NR}^9\text{R}^8$, or $-\text{COR}^{10}$ group, naphthyl, naphthyl
substituted by a C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CO_2R^8 ,
15 $-(\text{CH}_2)_m\text{OR}^8$, $-(\text{CH}_2)_m\text{NR}^8\text{R}^9$ or $-\text{COR}^{10}$, or heteroaryl;

Q is phenyl, naphthyl or heteroaryl, said phenyl, naphthyl
or heteroaryl group being optionally substituted by one
to three same or different C_{1-6} alkyl, C_{1-6} fluoroalkyl,
 C_{1-6} alkoxy, halogen, CO_2R^{11} , $-(\text{CH}_2)_q\text{OR}^{11}$,
20 $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or $-\text{COR}^{13}$ with the proviso
that when A is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or
 $-\text{O}-$, then Q is a phenyl, naphthyl or heteroaryl group
substituted by one to three halogen, C_{1-6} fluoroalkyl,
 CO_2R^{11} , $-(\text{CH}_2)_q\text{OR}^{11}$, $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or
25 $-\text{COR}^{13}$;

R⁵ and R⁶ are each independently hydrogen or C₁₋₆ alkyl;

5 R^8 and R^9 are each independently hydrogen or C_{1-6} alkyl;

R^{10} and R^{13} are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;

R^{11} and R^{12} are each independently hydrogen or C_{1-6} alkyl;

10

R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula



15

Z is hydrogen, C_{1-6} alkyl, benzyl, *p*-methoxybenzyl, allyl or trimethylsilylethyl;

m and q are independently 0 to 2;

20

p is 0 or 1 with the proviso that when p is 0 then Q is phenyl, naphthyl or heteroaryl substituted by one to three $-(CH_2)_qOR^{11}$, $-(CH_2)_qNR^{11}R^{12}$, or $-COR^{13}$;

25 R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

R^1 is $-CO_2Z$, C_{1-6} alkyl, $-CH_2OH$, $-CONHR^7$ or CHO ;

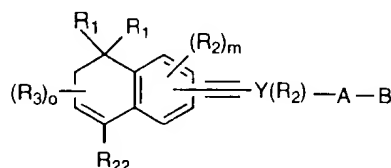
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R^7 is hydrogen or C_{1-6} alkyl;

provided that when X is $-C\equiv C-$, A is not $-CR^8 = CR^9-$ or $-C\equiv C-$.

The novel compounds of formula II are distinguished from those
 10 in WO 97/09297 by the presence of the linking group "A" between the core
 skeleton and the terminal aryl or heteroaryl substituent.

U.S. Patent 5,648,514 discloses retinoids of the formula



15

wherein

R_1 is hydrogen or alkyl of 1 to 10 carbons;

20 R_2 and R_3 are hydrogen, or alkyl of 1 to 6 carbons and the substituted
 ethynyl group occupies either the 2 or the 3 position of the
 dihydronaphthalene nucleus;

m is an integer having the value of 0-3;

25

o is an integer having the value 0-3;

5

Y is a phenyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, said groups being optionally substituted with one or two R_2 groups;

10

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

15

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, $-CH_2OR_{11}$, $-CH_2OCOR_{11}$, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons and

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R_{22} is hydrogen, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, alkynyl

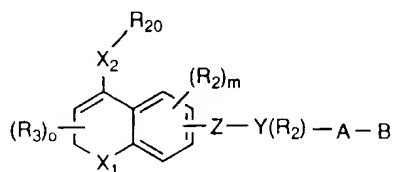
- 5 having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C_1 - C_{10} -alkylphenyl, naphthyl, C_1 - C_{10} -alkylnaphthyl, phenyl, C_1 - C_{10} alkyl, naphthyl- C_1 - C_{10} alkyl, C_1 - C_{10} -alkenylphenyl having 1 to 3 double bonds, C_1 - C_{10} -alkynylphenyl having 1 to 3 triple bonds, phenyl- C_1 - C_{10} alkenyl
- 10 having 1 to 3 double bonds, phenyl- C_1 - C_{10} alkynyl having 1 to 3 triple bonds, hydroxy alkyl of 1 to 10 carbons, hydroxyalkynyl having 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds, where the acyl group is represented by COR_{14} , CN, $CON(R_1)_2$, $(CH_2)_pCO_2R_8$ where p is an
- 15 integer between 0 to 10, or R_{22} is aminoalkyl or thioalkyl of 1 to 10 carbons, or a 5 or 6 membered heteroaryl group optionally substituted with a C_1 to C_{10} alkyl group having 1 to 3 heteroatoms, said heteroatoms being selected from a group consisting of O, S, and N, or R_{22} is represented by $(CH_2)_pXR_1$ or by $(CH_2)_pNR_1R_2$; where X is O or S, the R_{14} group is hydrogen, alkyl of 1
- 20 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bond, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C_1 - C_{10} -alkylphenyl, naphthyl, C_1 - C_{10} -alkylnaphthyl, phenyl- C_1 - C_{10} alkyl, or naphthyl- C_1 - C_{10} alkyl.

25

The novel compounds of formula II are distinguished from those in U.S. 5,648,514 by the nature of the linking group "X" which is not $C\equiv C$ linked to the central benzene ring when A is $-CR^8 = CR^9-$ or $-C\equiv C-$.

5

Published patent application WO 97/48672 discloses retinoids of the formula



Formula 5

- 10 wherein X_1 is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between 0 to 2;

Z is -N=N-,

-N(O)=N-,

15 -N=N(O)-,

-N=CR₁-,

-CR₁=N,

-(CR₁=CR₁)_{n'}- where n' is an integer having the value 0-5,

-CO-NR₁-,

20 -CS-NR₁-,

-NR₁-CO,

-NR₁-CS-,

-COO-,

-OCO-,

25 -CSO-,

- 5 -OCS-,
 -CO-CR₁=CR₁-;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro
 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or
 10 alkylthio of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0-3;

15

o is an integer having the value of 0-3;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group
 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
 20 thiazolyl, oxazolyl, imidazolyl and pyrrolazolyl, said phenyl and heteroaryl
 groups being optionally substituted with one or two R₂ groups, or

when Z is -(CR₁=CR₁)_n- and n' is 3, 4 or 5 then Y represents a direct
 valence bond between said (CR₂=CR₂)_n group and B;

25

A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons,
 cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2
 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

5

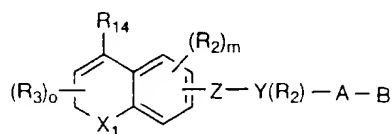
B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, -CH₂OR₁₁, -CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or Si(C₁₋₆alkyl)₃, where

- R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is
 10 an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
 15 alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons;

X₂ is O, S, SO or SO₂, and

- 20 R₂₀ is Si(C₁₋₆alkyl)₃, R₁₄, COR₁₄, SO₂R₂₁, where R₁₄ is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bond, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C₁-C₁₀-alkylphenyl, naphthyl, C₁-C₁₀-alkylnaphthyl, phenyl-C₁-C₁₀-alkyl, naphthyl-
 25 C₁-C₁₀-alkyl, or R₂₀ is hydroxyalkyl, aminoalkyl or thioalkyl having 1 to 10 carbons, and R₂₁ is alkyl of 1 to 10 carbons, fluoroalkyl of 1 to 10 carbons, or carbocyclic aryl selected from the group consisting of phenyl, C₁-C₁₀-alkylphenyl and phenyl-C₁-C₁₀-alkyl, and retinoids of the formula

-21-



Formula 6

5

wherein X_1 is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between 0 and 2;

10 Z is -N=N-,

-N(O)=N-,

-N=N(O)-,

-N=CR₁-,

-CR₁=N,

15 -(CR₁=CR₁)_{n'}- where n' is an integer having the value 0-5,

-CO-NR₁-,

-CS-NR₁-,

-NR₁-CO,

-NR₁-CS-,

20 -COO-,

-OCO-,

-CSO-,

-OCS-,

-CO-CR₁=CR₁-;

25

- 5 R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

10

m is an integer having the value of 0-3;

o is an integer having the value of 0-3;

- 15 Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups, or

- 20 when Z is $-(CR_1=CR_1)_{n'}$ and n' is 3, 4 or 5 then Y represents a direct valence bond between said $(CR_2=CR_2)_{n'}$ group and B;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2

- 25 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, $-CH_2OR_{11}$, $-CH_2OCOR_{11}$, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$,

- 5 -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or Si(C₁₋₆alkyl)₃, where
 R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is
 an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl
 group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is
 phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an
 10 alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or
 phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower
 alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5
 carbons; and
- 15 R₁₄ is (R₁₅)_r-substituted alkyl of 1-6 carbons, (R₁₅)_r-substituted alkenyl of 1-6
 carbons and 1 or 2 double bonds, (R₁₅)_r-substituted alkynyl of 1-6 carbons
 and 1 or 2 triple bonds, (R₁₅)_r-phenyl, (R₁₅)_r-naphthyl, or (R₁₅)_r-heteroaryl
 where the heteroaryl group has 1 to 3 heteroatoms selected from the
 group consisting of O, S and N, r is an integer having the values of 0-5,
 20 and
- R₁₅ is independently H, F, Cl, Br, I, NO₂, N(R₈)₂, N(R₈)COR₈,
 NR₈CON(R₈)₂, OH, OCOR₈, OR₈, CN, COOH, COOR₈ an alkyl group
 having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10
 25 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds,
 alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a
 (trialkyl)silyl or (trialkyl)silyloxy group where the alkyl groups
 independently have 1 to 6 carbons.

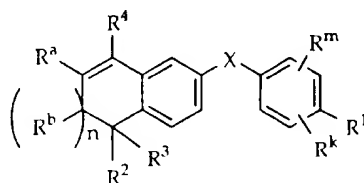
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The novel compounds of formula II may be distinguished from those in WO 97/48672, formula 5, by the nature of the linking group "A" versus "X₂". The formula II compounds may be distinguished from those in WO 97/48672, formula 6, by the inclusion of the linking group "A" between the core skeleton and the terminal aryl or heteroaryl substituent.

SUMMARY OF THE INVENTION

The present invention provides a method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering an effective amount of a retinoid antagonist for a period of time sufficient to permit tissue repair.

In a preferred embodiment the retinoid antagonist used in the above method is a compound having the general formula



IA

or a nontoxic pharmaceutically acceptable salt, physiologically hydrolyzable ester and solvate thereof, in which

25

5

X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
 -NHCH₂- or -CR⁵ = CR⁶-;

10 R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆alkyloxy or nitro;

n is zero or one;

R⁴ is -(CH₂)_t-Y;

R¹ is -CO₂Z, -C₁₋₆ alkyl, CH₂OH, -CONHR^y or CHO;

15 R² and R³ are independently hydrogen or C₁₋₆ alkyl;

R^a and R^b are independently hydrogen or C₁₋₆ alkyl; but when n is
 one, R^a and R^b together can form a radical of the
 formula



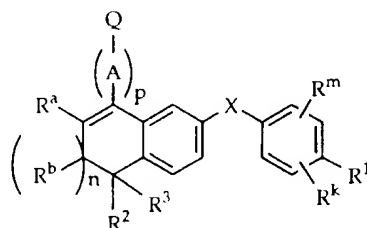
20 Y is phenyl or naphthyl and both radicals can be optionally
 substituted with one to three same or different C₁₋₆
 alkyl or halogen groups;

Z is hydrogen or C₁₋₆ alkyl;

R⁵, R⁶ and R^y are independently hydrogen or C₁₋₆ alkyl; and

25 t is zero to six.

5 In another aspect, the present inventors have prepared a novel series of substituted (5,6)-dihydronaphthalenyl compounds which also are potent retinoid antagonists. These new compounds display the utilities of the retinoid antagonist compounds described in U.S. Patent 5,618,839 and EP 661,259 A1, and also possess the ability to prevent or minimize post-
 10 surgical adhesion formation. This new series of retinoid antagonists is generically defined by the formula



II

15 or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable esters or solvates thereof, in which

X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 20 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
 -NHCH₂- or -CR⁵ = CR⁶;
 R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆ alkyloxy or nitro;
 n is zero or one;

- 5 A is $-\text{NH}(\text{CH}_2)_m-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{O}-$, $-\text{C}\equiv\text{C}-$, $-\text{CR}^8\text{R}^9$,
 $-\text{CR}^8 = \text{CR}^9$, phenyl, phenyl substituted by a C_{1-6} alkyl,
 C_{1-6} alkoxy, halogen, CO_2R^8 , $-(\text{CH}_2)_m\text{OR}^8$, $-(\text{CH}_2)_m\text{NR}^9\text{R}^8$,
or $-\text{COR}^{10}$ group, naphthyl, naphthyl substituted by a
 C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CO_2R^8 , $-(\text{CH}_2)_m\text{OR}^8$,
10 $-(\text{CH}_2)_m\text{NR}^8\text{R}^9$ or $-\text{COR}^{10}$, or heteroaryl;
- Q is phenyl, naphthyl or heteroaryl, said phenyl, naphthyl
or heteroaryl group being optionally substituted by one
to three same or different C_{1-6} alkyl, C_{1-6} fluoroalkyl,
 C_{1-6} alkoxy, halogen, CO_2R^{11} , $-(\text{CH}_2)_q\text{OR}^{11}$,
15 $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or $-\text{COR}^{13}$ with the proviso
that when A is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{O}-$, then Q is a
phenyl, naphthyl or heteroaryl group substituted by
one to three halogen, C_{1-6} fluoroalkyl, CO_2R^{11} ,
 $-(\text{CH}_2)_q\text{OR}^{11}$, $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or $-\text{COR}^{13}$;
20
- R^5 and R^6 are each independently hydrogen or C_{1-6} alkyl;
- R^8 and R^9 are each independently hydrogen or C_{1-6} alkyl;
- 25 R^{10} and R^{13} are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;
- R^{11} and R^{12} are each independently hydrogen or C_{1-6} alkyl;

-28-

- 5 R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula



- 10 Z is hydrogen, C_{1-6} alkyl, benzyl, p-methoxybenzyl, allyl or trimethylsilylethyl;

m and q are independently 0 to 2;

- 15 p is 0 or 1 with the proviso that when p is 0 then Q is phenyl, naphthyl or heteroaryl substituted by one to three $-(CH_2)_qOR^{11}$, $-(CH_2)_qNR^{11}R^{12}$, or $-COR^{13}$;

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

20

R^1 is $-CO_2Z$, C_{1-6} alkyl, $-CH_2OH$, $-CONHR^7$ or CHO ;

R^7 is hydrogen or C_{1-6} alkyl;

provided that when X is $-C\equiv C-$, A is not $-CR^8 = CR^9-$ or $-C\equiv C-$.

25

The new retinoid antagonists of formula II are useful as anti-inflammatory agents for treatment of chronic skin inflammatory diseases

5 such as psoriasis and atopic dermatitis, as agents for the treatment of
rheumatic diseases such as rheumatoid arthritis, as antitumor agents for
the treatment of various tumors as well as non-malignant proliferative
skin diseases, and as agents for the minimization or prevention of post-
surgical adhesion formation.

10

DESCRIPTION OF THE DRAWING

FIG. 1 shows the number and severity of caecal adhesions in rat
after oral administration of a preferred retinoid antagonist of the present
15 invention.

DETAILED DESCRIPTION OF THE INVENTION

Adhesion formation, particularly following peritoneal surgery, is a
20 major source of postoperative morbidity and mortality. Appendectomy
and gynecologic surgery are the most frequent surgical procedures
implicated in clinically significant adhesion formation. The most serious
complication of intraperitoneal adhesions is intestinal obstruction. In
addition, adhesions are associated with chronic or recurrent pelvic pain
25 and infertility in females.

5 Various approaches for the prevention of adhesion formation have been explored, but an effective therapeutic approach has not been discovered to date.

 The use of retinoids for prevention of adhesion formation is described in U.S. Patent 5,534,261. While the term "retinoid" as used in this patent is defined in several ways, it appears that the inventors intended this term to refer to retinoid agonists, as the specific embodiments and preferred compounds are all of this class. No mention is made of retinoid antagonists or whether such antagonists would have
10 this desirable property.
15

 The present inventors have unexpectedly found that retinoid antagonists possess utility to prevent or minimize adhesion formation and, in fact, appear to be significantly more effective for this use than
20 retinoid agonists. Moreover, the retinoid antagonists are less toxic than retinoid agonists in that, unlike the agonists, they do not appear to induce hypervitaminosis A, a syndrome which can result in death.

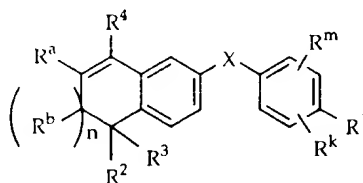
 Thus, in one aspect, the present invention provides a method for
25 the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering an effective amount of a retinoid antagonist for a period of time sufficient to permit tissue repair.

5 In its broadest aspect, any retinoid antagonist as defined herein can be employed. The literature provides several examples of suitable retinoid antagonists. For example, retinoid antagonists are described in Journal of the Pharmaceutical Society of Japan, Vol. 114, Issue 11, pages 847-862 (1994), in Proc. Natl. Acad. Sci. USA, Vol. 91, Issue 12, pages 5632-
10 5636 (1994), in J. Biol. Chem., Vol. 271, Issue 21, pages 12209-12212 (1996), in J. Med. Chem., Vol. 38, pages 4764-4767 (1995), in J. Med. Chem., Vol. 37, pages 1508-1517 (1994), in Proc. Natl. Acad. Sci. USA, Vol. 89, pages 7129-7133 (1992), in Med. Chem. Res., Vol. 1, pages 220-225 (1991), in J. Med. Chem., Vol. 38, pages 3163-3173 (1995), and in J. Biol. Chem., Vol. 20, pages
15 11897-11903 (1996). Other retinoid antagonists can be found by using the assay procedures described below. Applicants believe that prior to their invention, no retinoid antagonists have been disclosed as having a therapeutic utility.

20 As noted above, the term "retinoid antagonist" as used herein means a compound which binds to all three of the retinoic acid receptor subtypes RAR α , RAR β and RAR γ but does not activate at least two of the three RAR receptor subtypes in a standard retinoid transactivation assay. Suitable binding and transactivation assays are disclosed in Proc. Natl.
25 Acad. Sci. USA, Vol. 92, pg. 1812-1816, 1995. Functional antagonism is also illustrated in, for example, J. Med. Chem., 38, 4764-4767 (1995), where the transactivation activity of retinoic acid is inhibited by increasing concentrations of the antagonist.

5

A preferred embodiment of the present invention is the use in the above method of a retinoid antagonist having the general formula



IA

10

or a nontoxic pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof, in which

- X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 15 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
 -NHCH₂- or -CR⁵ = CR⁶;
- R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆alkyloxy or nitro;
- 20 n is zero or one;
- R⁴ is -(CH₂)_i-Y;
- R¹ is -CO₂Z, -C₁₋₆ alkyl, CH₂OH, -CONHR^y or CHO;
- R² and R³ are independently hydrogen or C₁₋₆ alkyl;

- 5 R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula



- Y is phenyl or naphthyl and both radicals can be optionally substituted with one to three same or different C_{1-6} alkyl or halogen groups;
- 10 Z is hydrogen or C_{1-6} alkyl;
- R^5 , R^6 and R^7 are independently hydrogen or C_{1-6} alkyl; and
- t is zero to six.

15

- In the present application, the numbers in subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example, C_{1-6} alkyl refers to straight and branched chain alkyl groups with one to six carbon atoms. For example, methyl, ethyl,
- 20 n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, n-hexyl, 3-methylpentyl, etc. and C_{3-6} cycloalkyl refers to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The term "halogen" refers to fluorine, chlorine, bromine or iodine.

- 25 Some compounds of formula IA may also form pharmaceutically acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. These salts are

- 5 also part of the present invention. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, and aluminum salts. The sodium or potassium salts are preferred. Amines which are capable of forming stable salts group include trialkylamines such a triethylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-ephedrine, 10 N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine, or the like pharmaceutically acceptable amines.

- When a compound of formula IA contains a carboxy group, it can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula IA compounds per se. They are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester per se is active, or in those 20 instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula IA include C₁₋₆alkyl, benzyl, 4-methoxybenzyl, indanyl, phthalidyl, methoxymethyl, C₁₋₆alkanoyloxy, C₁₋₆alkyl, e.g. acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkyl, e.g. 25 methoxycarbonyloxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well-known physiologically hydrolyzable esters used,

5 for example, in the penicillin and cephalosporin arts. Such esters are prepared by conventional techniques known in the art.

The structural formulae as drawn in the instant application are believed to best represent the structures of compounds of the present
10 invention. However, some compounds within the scope of the invention may exist as other tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the structural formulae represent all
15 tautomeric forms, insofar as they may exist.

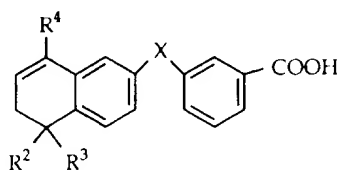
The term "organ surface" is intended to encompass any internal organ of a living animal including but not limited to the uterus, intestines, liver, kidneys, heart and lungs.
20

The method of the present invention is applicable to all living animals. The preferred "subject" for the application of the invention is, however, a mammal. The most preferred subjects are humans.

25 A preferred embodiment of the present invention comprises the above-described method of preventing surgical adhesions wherein the retinoid antagonist is a compound of the formula

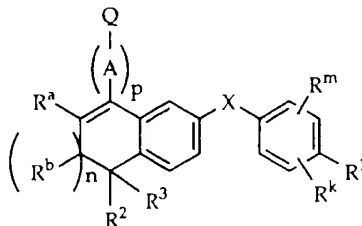
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5



in which R^2 and R^3 are each independently C_{1-6} alkyl, X is $-CR^5=CR^6-$ in which R^5 and R^6 are each independently hydrogen or C_{1-6} alkyl, and R^4 is $-(CH_2)_t-Y$ in which t is 0 and Y is phenyl, phenyl substituted by 1-3 same or different halogen or C_1-C_6 alkyl substituents, or naphthyl.

In another aspect the present invention provides a new series of retinoid antagonist compounds of the formula



15

II

or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable esters or solvates thereof, in which

X is $-O-CO-$, $-NH-CO-$, $-CS-NH-$, $-CO-O-$, $-CO-NH-$, $-COS-$,
 $-SCO-$, $-SCH_2-$, $-CH_2-CH_2-$, $-C\equiv C-$, $-CH_2-NH-$,
 $-COCH_2-$, $-NHCS-$, $-CH_2S-$, $-CH_2O-$, $-OCH_2-$,
 $-NHCH_2-$ or $-CR^5 = CR^6-$;

20

- 5 R^m and R^k are independently hydrogen, halogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy or nitro;
- n is zero or one;
- A is $-NH(CH_2)_m-$, $-S-$, $-SO-$, $-SO_2-$, $-O-$, $-C\equiv C-$, $-CR^8R^9$,
 $-CR^8 = CR^9-$, phenyl, phenyl substituted by a C_{1-6} alkyl,
 10 C_{1-6} alkoxy, halogen, CO_2R^8 , $-(CH_2)_mOR^8$,
 $-(CH_2)_mNR^9R^8$, or $-COR^{10}$ group, naphthyl, naphthyl
 substituted by a C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CO_2R^8 ,
 $-(CH_2)_mOR^8$, $-(CH_2)_mNR^8R^9$ or $-COR^{10}$, or heteroaryl;
- Q is phenyl, naphthyl or heteroaryl, said phenyl, naphthyl
 15 or heteroaryl group being optionally substituted by one
 to three same or different C_{1-6} alkyl, C_{1-6} fluoroalkyl,
 C_{1-6} alkoxy, halogen, CO_2R^{11} , $-(CH_2)_qOR^{11}$,
 $-(CH_2)_qNR^{11}R^{12}$, $-NHCOR^{13}$ or $-COR^{13}$ with the proviso
 that when A is $-S-$, $-SO-$, $-SO_2-$ or $-O-$, then Q is a
 20 phenyl, naphthyl or heteroaryl group substituted by
 one to three halogen, C_{1-6} fluoroalkyl, CO_2R^{11} ,
 $-(CH_2)_qOR^{11}$, $-(CH_2)_qNR^{11}R^{12}$, $-NHCOR^{13}$ or $-COR^{13}$;

R^5 and R^6 are each independently hydrogen or C_{1-6} alkyl;

25

R^8 and R^9 are each independently hydrogen or C_{1-6} alkyl;

R^{10} and R^{13} are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;

5

R^{11} and R^{12} are each independently hydrogen or C_{1-6} alkyl;

R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula

10



Z is hydrogen, C_{1-6} alkyl, benzyl, *p*-methoxybenzyl, allyl or trimethylsilylethyl;

15

m and q are independently 0 to 2;

p is 0 or 1 with the proviso that when p is 0 then Q is phenyl, naphthyl or heteroaryl substituted by one to three $-(CH_2)_qOR^{11}$, $-(CH_2)_qNR^{11}R^{12}$, or

20

$-COR^{13}$

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

R^1 is $-CO_2Z$, C_{1-6} alkyl, $-CH_2OH$, $-CONHR^7$ or CHO ;

25

R^7 is hydrogen or C_{1-6} alkyl;

provided that when X is $-C\equiv C-$, A is not $-CR^8 = CR^9-$ or $-C\equiv C-$.

5

The meanings of the substituent groups for the formula II compounds as well as the meanings for the terms "pharmaceutically acceptable salts and physiologically hydrolyzable esters" are, unless otherwise stated, the same as those described above for the formula IA compounds. The term "heteroaryl" as used herein includes mono-, bi- and polycyclic aromatic heterocyclic groups containing 1-4 O, N or S atoms; preferred are 5- and 6-membered heterocyclic groups such as thienyl, furyl, thiadiazolyl, oxadiazolyl, triazolyl, isothiazolyl, thiazolyl, imidazolyl, isoxazolyl, tetrazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, 10 pyridazinyl, pyrrolyl, pyrazolyl, etc. and fused 5,6-membered and 6,6-membered aromatic heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, indazolyl, indoliziny, isoquinolyl, quinolyl, naphthyridinyl, quinoxaliny, quinazolinyl, 15 pteridinyl etc.

20

The retinoid antagonists of general formula IA may be made by the procedures disclosed in co-pending U.S. Patent 5,618,839 and in EP 661,259 A1 published July 5, 1995.

25

The retinoid antagonists of general formula II may be made by known procedures. Suitable reaction schemes for preparing the formula II compounds are illustrated below.

5 As used herein and in the reaction schemes, the term "enol triflate or silyl formation" is intended to include conventional and well-known enolate formation procedures and subsequent trapping of this enolate by the well-known triflating or silylating agents. Thus the ketones are treated with an organic base such as 2,6-di-tert-butyl-4-methyl-pyridine,
10 sodium hydride, potassium hydride, lithium diisopropylamide or lithium bis(trimethylsilyl)amide in an inert organic solvent such as tetrahydrofuran, dimethylformamide or dichloromethane and the like. The resulting enolates are then treated with triflic anhydride or 2-[N,N-bis(trifluoromethyl-sulfonyl)amino]pyridine and the like or an
15 alkylsilyl chloride.

 As used herein and in the reaction schemes, the term "Stille, Negishi or Suzuki-type coupling" is intended to include all the known cross-coupling methods that involve the reaction of an enol triflate with a
20 tin, zinc, magnesium or boronic derivative catalyzed with a palladium(0) or paladium(II) catalyst such as tetrakis(triphenylphosphine)palladium(0), bistris(triphenylphosphine)palladium(II) chloride, palladium(II) acetate, palladiumtris(dibenzylidene-acetone)di-palladium(0), bis(diphenylphosphineferrocene)palladium(II) chloride and
25 the like or a nickel(0) or nickel(II) catalyst such as tetrakis(triphenylphosphine)-nickel(0), bistris(triphenylphosphine)nickel(II) chloride and the like. Very often, as known by those skilled in the art, copper iodide, lithium chloride, zinc chloride or triphenylarsine, tris(2-

5 furyl)phosphine or tri(2,4,6-trimethoxy-phenyl)phosphine must be added. These reactions are performed in an inert organic solvent such as dioxane, N-methylpyrrolidone, dimethylformamide, dimethoxyethane, tetrahydrofuran, toluene, benzene and the like.

10 As used herein and in the reaction schemes, the term "Heck coupling" is intended to include all known vinylations of alkenes or alkynes. Thus, a vinyl triflate reacts with various substituted or non-substituted alkenes or alkynes in the presence of a trialkylamine base or an inorganic base such as potassium carbonate, sodium acetate and the
15 like and a catalytic amount of Pd(II) complex such as palladium(II) acetate, bistrisphenylphosphinepalladium(II) chloride or bisacetonitrilepalladium(II) chloride. Sometimes a phosphine ligand may facilitate the reaction such as triphenylphosphine, tritolylphosphine, diphenylphosphineferrocene or diphenylphosphinepropane and the like.

20

As used herein and in the reaction schemes the term "hydrolysis" is intended to include conventional hydrolysis procedures of esters well-known to those skilled in the art. For example, methyl or ethyl esters may be removed by the use of aqueous solutions of sodium or potassium
25 alkoxides in tetrahydrofuran or ethanol. The hydrolysis of tert-butyl esters is carried out under acidic conditions such as 90% trifluoroacetic acid or 6N hydrochloric acid in solvents such as tetrahydrofuran or dichloromethane. Allyl esters may be removed by the use of a Pd(0)

5 catalyst such as tetrakis(triphenylphosphine)palladium(0) and a nucleophile such as sodium acetate, potassium or sodium 2-ethylhexanoate, pyrrolidine or morpholine and the like in an organic solvent such as acetonitrile, tetrahydrofuran, dichloromethane and the like. Finally, silyl esters or ethyltrimethylsilyl esters may be cleaved by the
10 use of tetrabutylammonium fluoride in tetrahydrofuran. The term "hydrolysis" is also intended to include conventional hydrolysis procedures of alcohol protecting groups. For example, the hydrolysis of a p-methoxybenzyl, methoxymethyl, methyl ethers and the like may be carried out under acidic conditions such as 90% trifluoroacetic acid, 3N
15 hydrochloric acid, sulfuric acid or boron tribromide in solvents such as dichloromethane, tetrahydrofuran, acetic acid and the like. Furthermore, organosilyl blocking groups such as tert-butyldimethylsilyl and triethylsilyl may advantageously be removed by the use of tetrabutylammonium fluoride in tetrahydrofuran.

20

As used herein and in the reaction schemes the term "acylation" is intended to include conventional and well-known acylation procedures for the preparation of amides, esters or thioesters such as the use of leaving groups and activating groups in organic solvents such as
25 tetrahydrofuran, dichloromethane or mixture of aqueous-organic solvents in the presence of a base such as triethylamine, pyridine, dimethylaminopyridine and the like.

5 As used herein and in the reaction schemes the term "reduction" is intended to include well-known reduction procedures for aromatic nitro compounds or carbon-carbon multiple bonds such as reducing metals, i.e., activated zinc, iron or tin in presence of an acid such as acetic acid, hydrogen and palladium or sodium borohydride in presence of a nickel(II)
10 or cobalt(II) catalyst. The term "reduction" is also intended to include well-known reduction procedures for the ester groups such as aluminum or boron hydrides.

 As used herein and in the reaction schemes, the term "reductive
15 amination" is intended to include the well-known reaction of an amine with an aldehyde in acidic conditions or in presence of titaniumisopropoxide to give the Schiff base which is then reduced with sodium cyanoborohydride or sodium borohydride in ethanol.

20 As used herein and in the reaction schemes the term "alkylation" is intended to include conventional and well-known alkylation procedures. Thus, the desired hydroxy or thiol groups which are to be alkylated are treated in the presence of an organic or inorganic base such as sodium hydride, potassium hydride, lithium diisopropylamine or lithium
25 bis(trimethylsilyl)amide in an inert organic solvent such as tetrahydrofuran, dimethylformamide, hexamethylphosphoramide, dimethylsulfoxide, N-methylpyrrolidinone and the like with an alkylating agent such as an alkyl, allyl or benzyl halide, mesylate or tosylate. The

5 term "alkylation" is also intended to include conventional procedures involving the formation of an alkyl ketone from a carboxylic acid by the use of various alkyllithium reagents followed by trimethylsilyl chloride in an inert organic solvent such as tetrahydrofuran, dimethylformamide, N-methylpyrrolidinone and the like.

10

As used herein and in the reaction schemes the term "substitution" is intended to include well-known transformation procedures of an hydroxy group to an alkylsulfonate or arylsulfonate group such as methanesulfonate (mesylate), trifluoromethanesulfonate (triflate) and
15 p-toluenesulfonate (tosylate). These well known procedures involve for example the use of alkylsulfonyl or arylsulfonyl chlorides or anhydrides in an organic solvent such as dichloromethane or tetrahydrofuran in the presence of a base such as triethylamine, pyridine, dimethylaminopyridine, 2,6-di-tert-butyl-4-methyl-pyridine and the like.

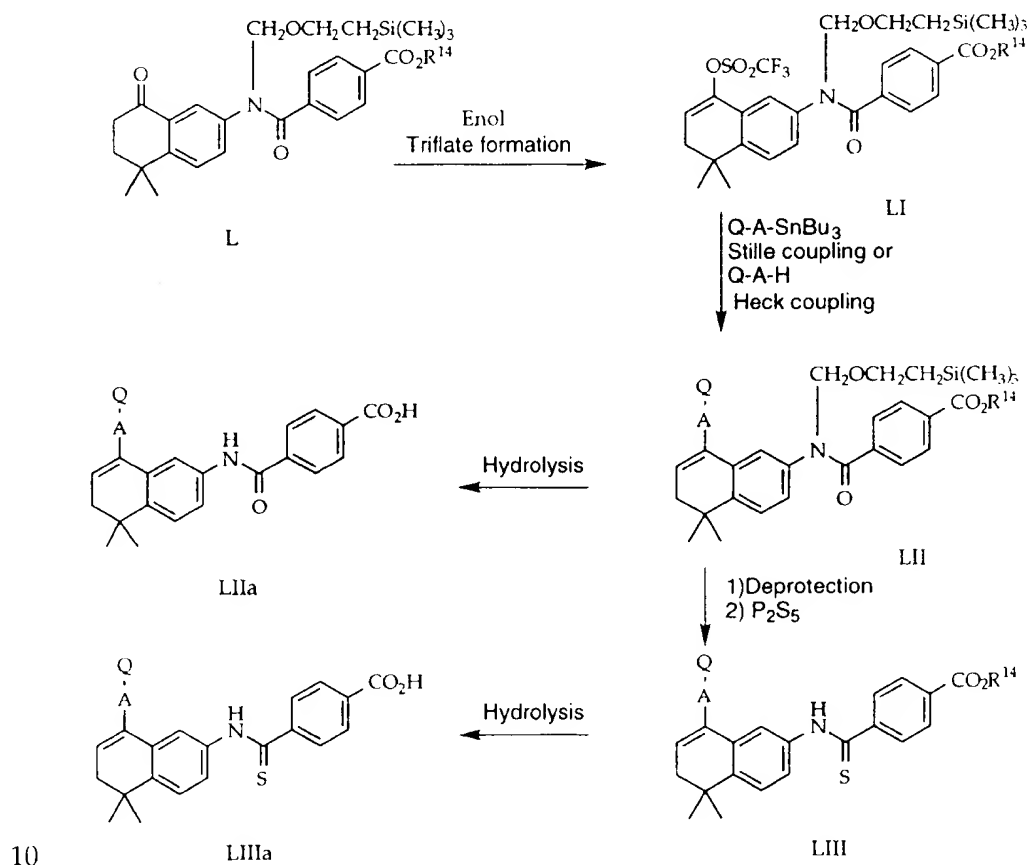
20 The term "substitution" is also intended to include well-known conversion procedures of a hydroxy group to a halide group such as chloride, bromide or iodide by the use of carbon tetrachloride or carbon tetrabromide in the presene of triphenylphosphine, or sodium iodide in an organic solvent such as acetone, dimethylformamide and the like.

25

As used herein and in the reaction schemes, the term "Horner-Emmons reaction" is intended to include conventional methods of Horner-Emmons olefination reactions of aldehydes or ketones by the use

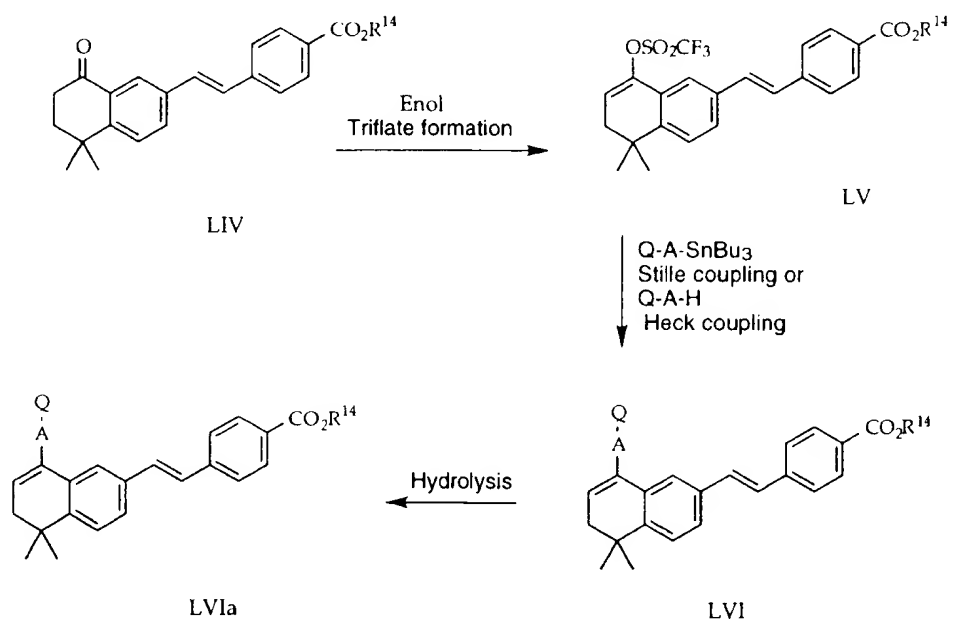
- 5 of an alkyl or aryl phosphonate and a base such as sodium hydride, lithium diisopropylamide or lithium bis(trimethylsilyl)amide and the like in an inert organic solvent such as tetrahydrofuran, dichloromethane, benzene and the like.

SCHEME 1



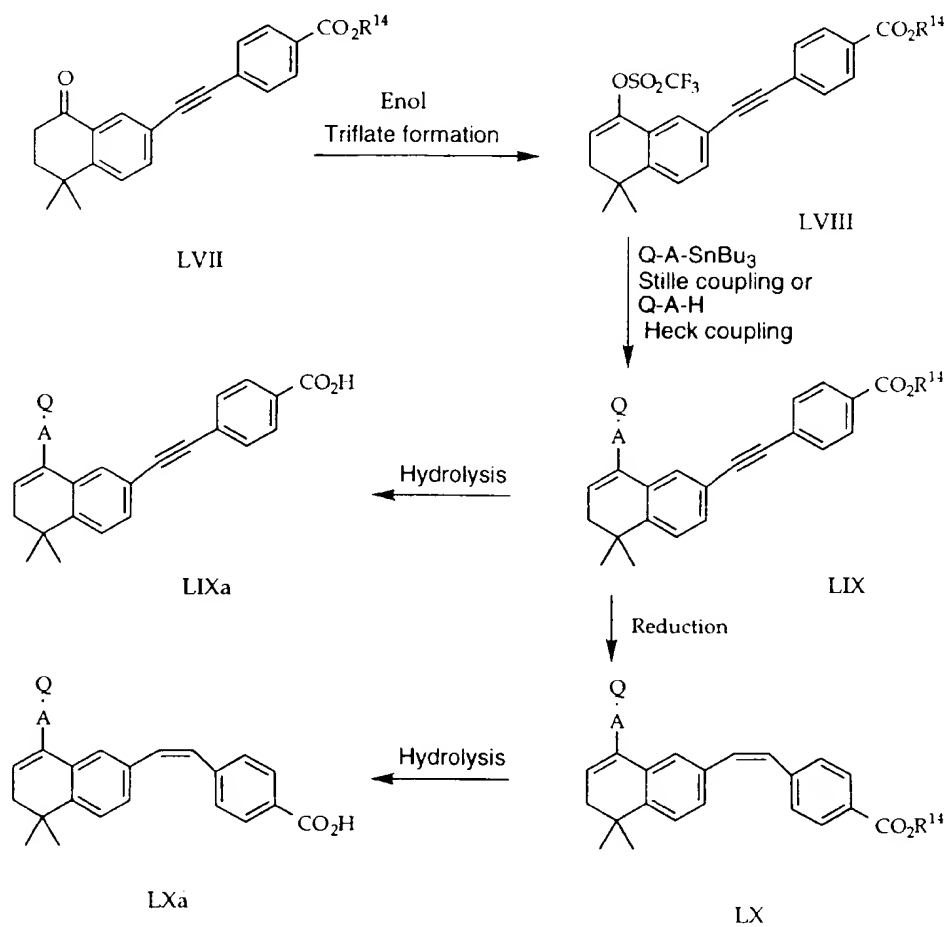
R^{14} = carboxyl protecting group

SCHEME 2

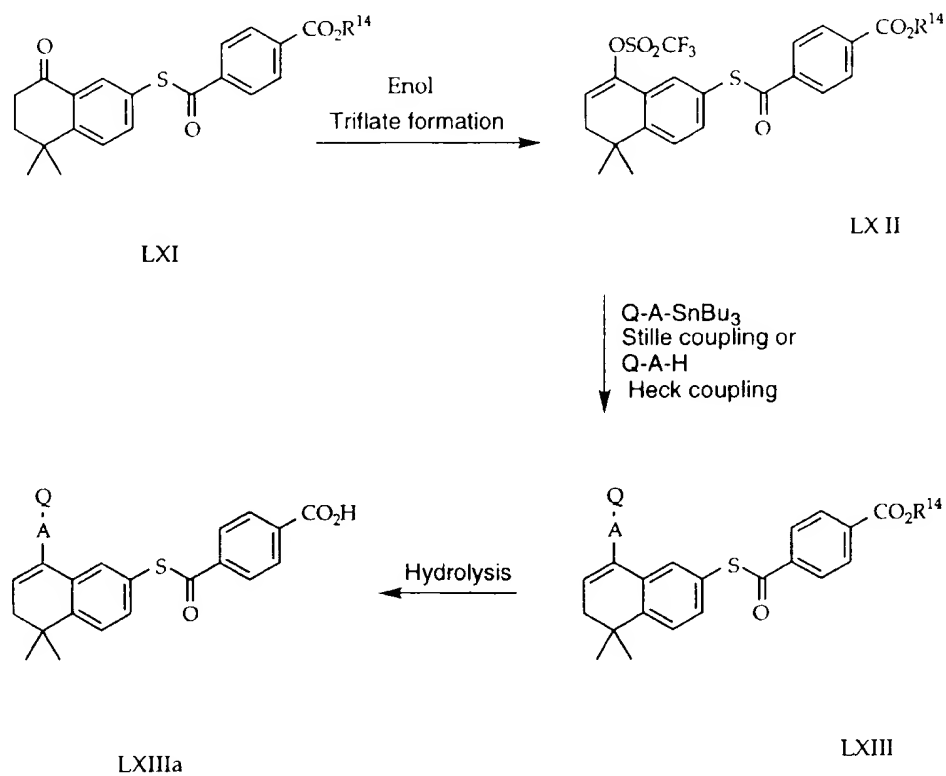


-47-

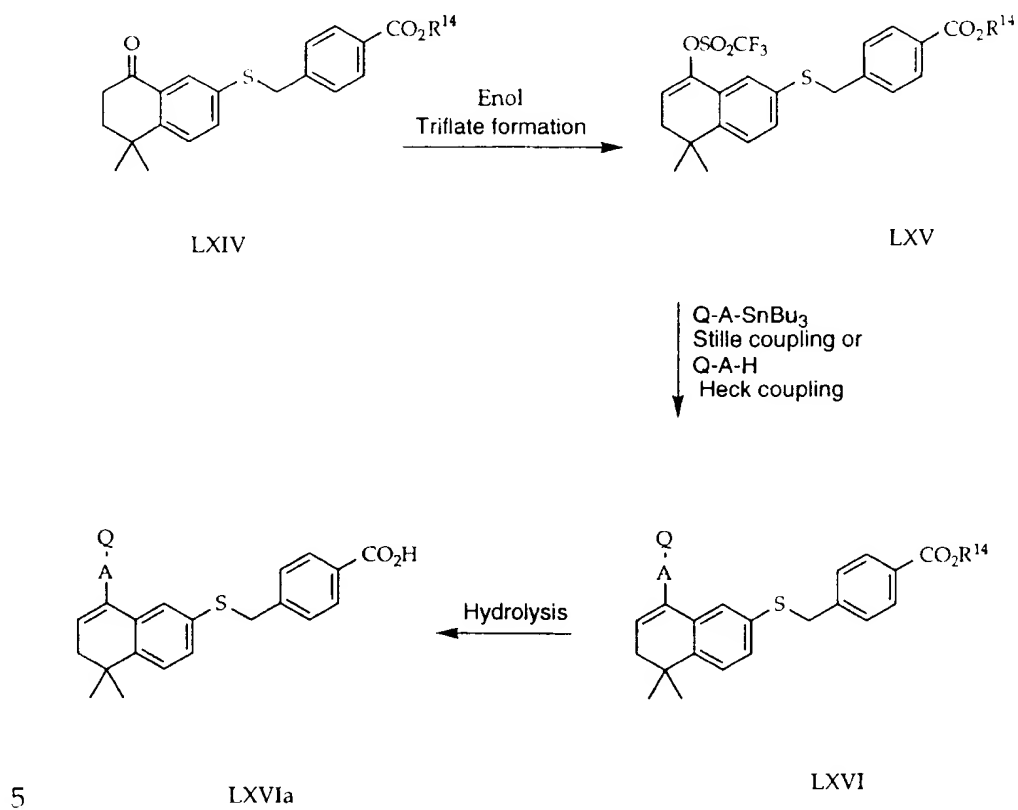
SCHEME 3



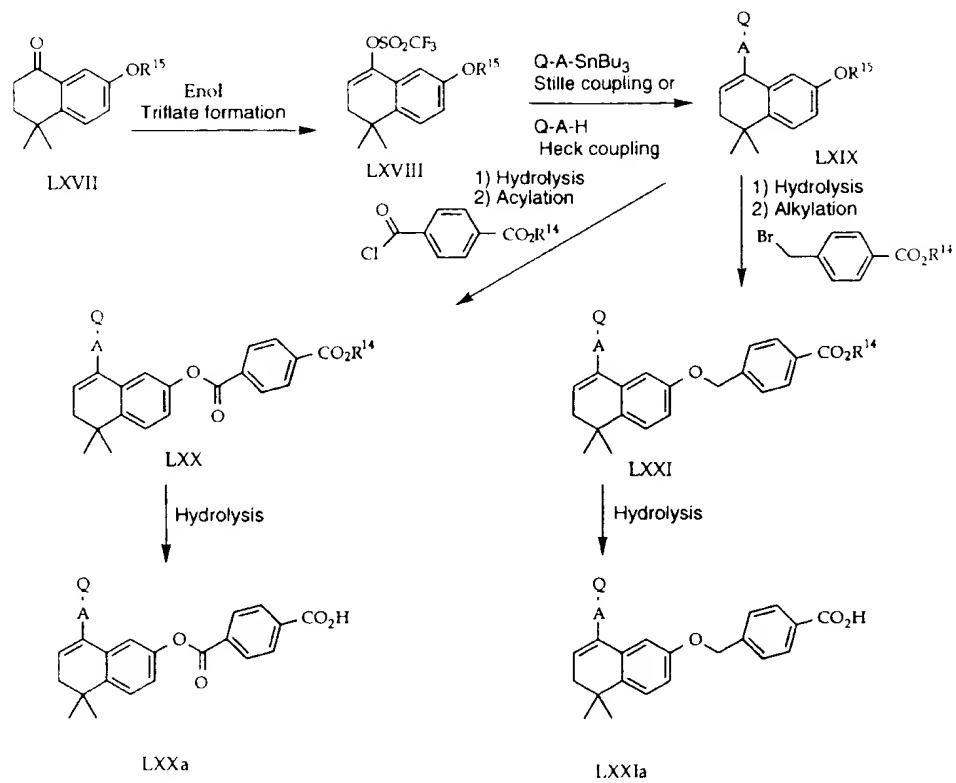
SCHEME 4



SCHEME 5



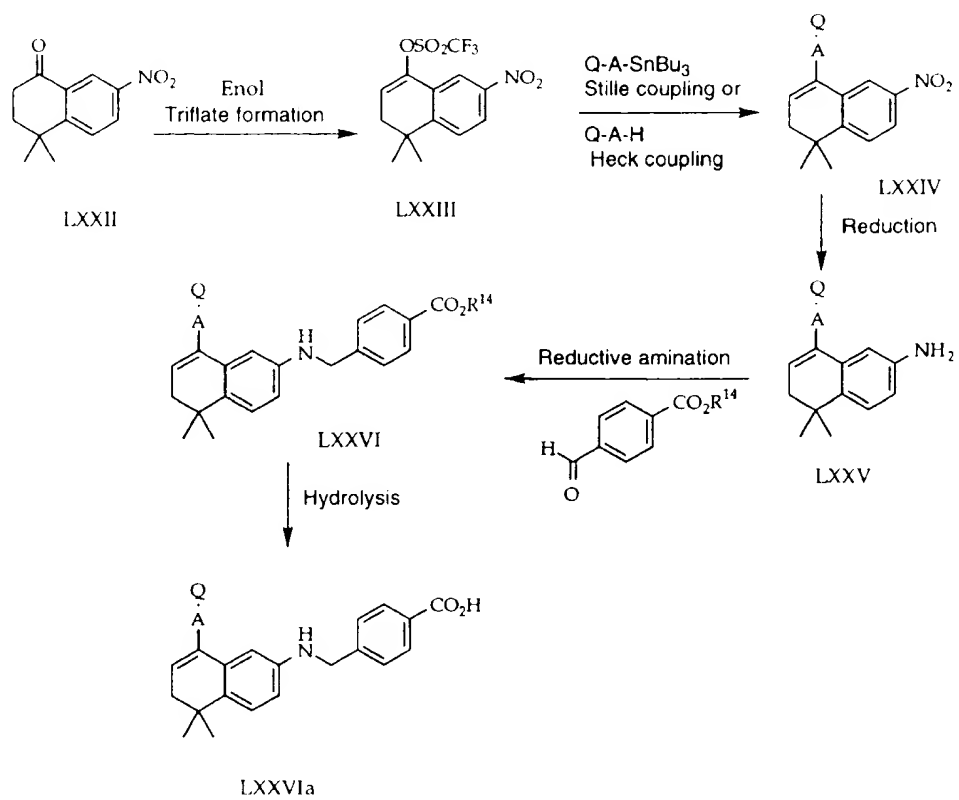
SCHEME 6



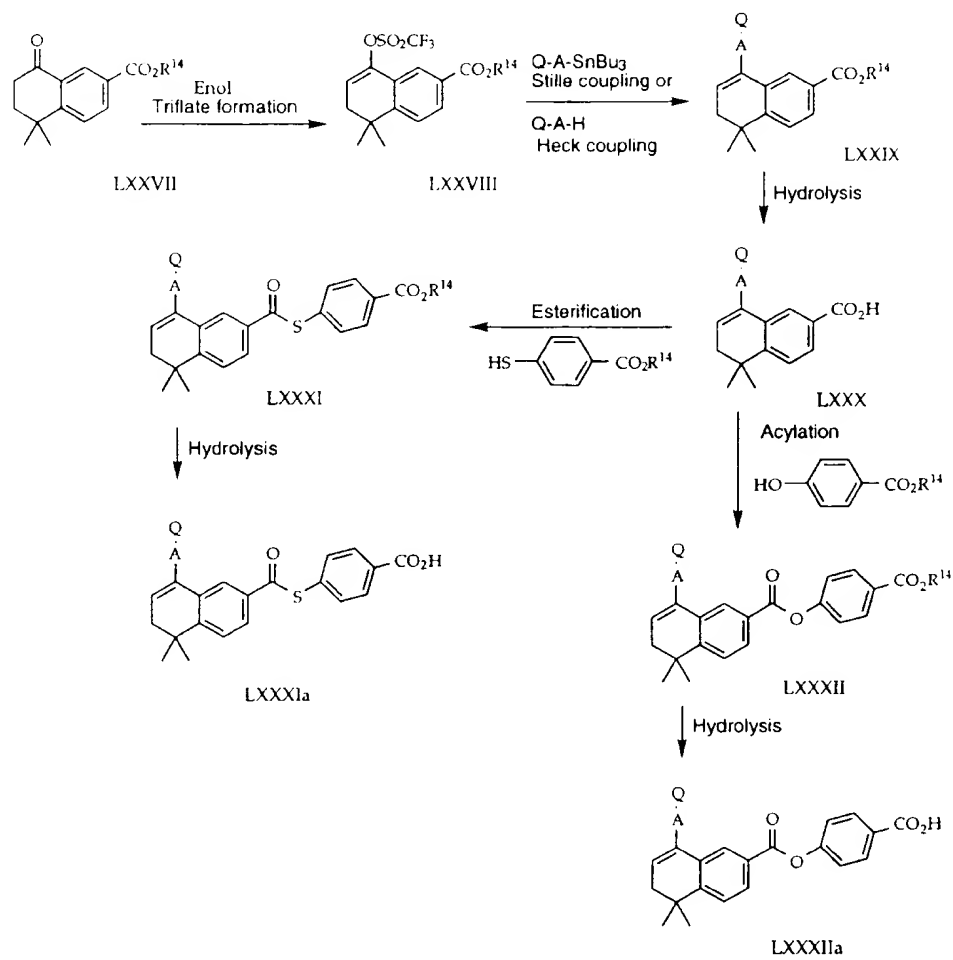
R¹⁵ = ether protecting group

-51-

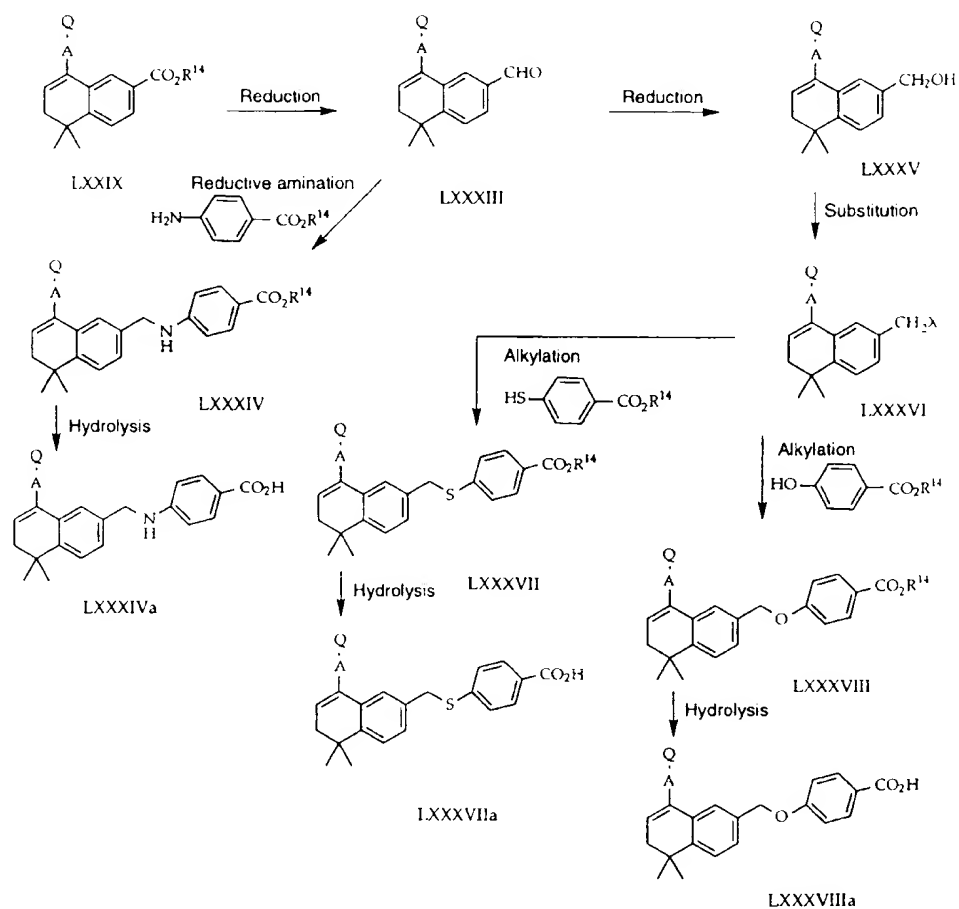
SCHEME 7



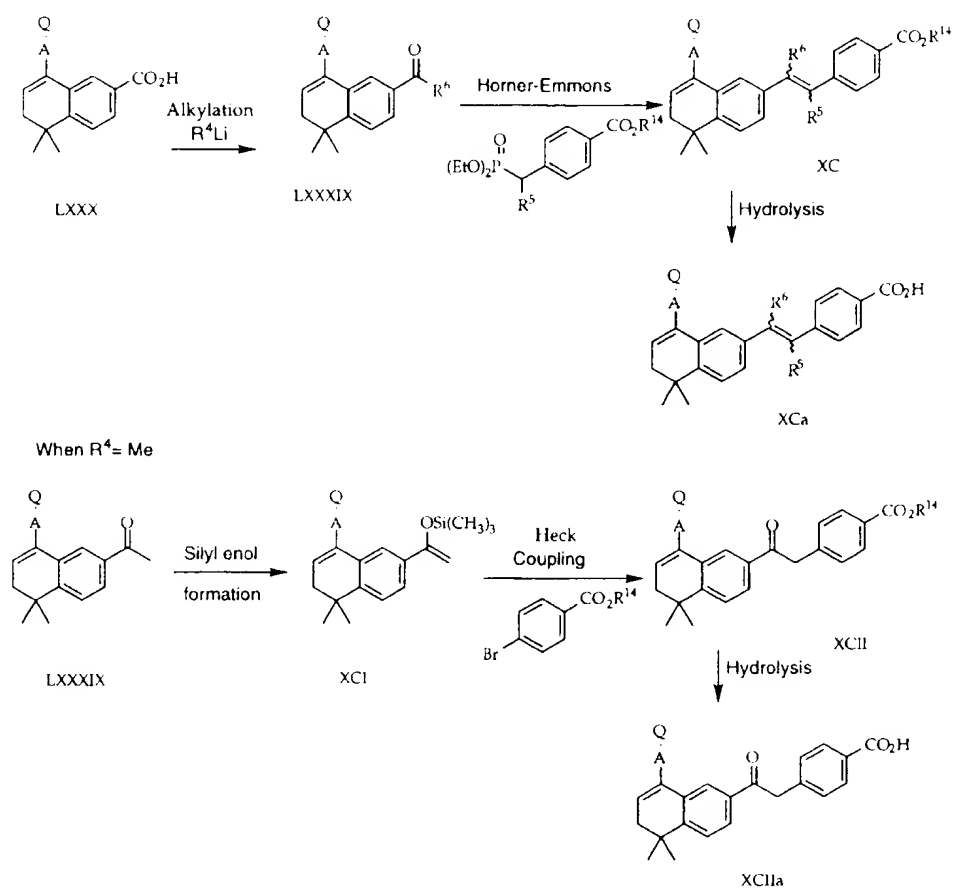
SCHEME 8



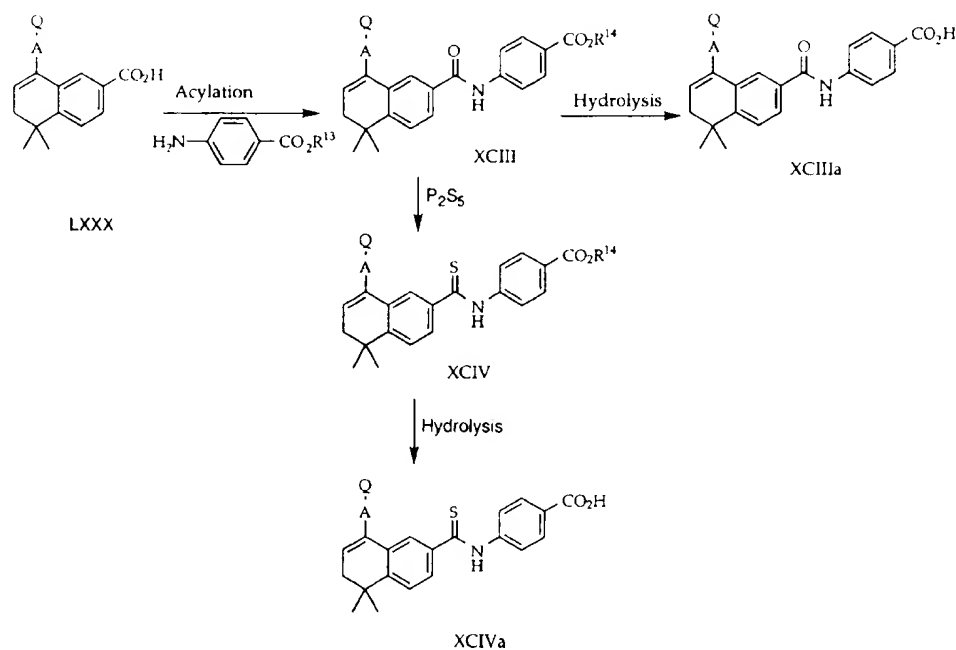
SCHEME 9



SCHEME 10



SCHEME 11



5

SCHEME 1-2

(II, where X = -NHCO-, -NHCS-, OR -CH=CH-)

- 10 Compound L (from European Patent application 661,259) is converted via base and a source of CF_3SO_2^- (as, for example, trifluoromethanesulfonic anhydride or 2-(N,N-di(trifluoromethanesulfonamido)pyridine) into the corresponding trifluoromethanesulfonate ("triflate") LI, to which the side chain is then
- 15 appended via, for example, Stille-type or Heck-type coupling to give protected ester LII. The protecting groups can then be cleaved off using procedures known in the art to give LIIa (II, X = NHCO). Alternatively, LII can be converted via deprotection of the amide nitrogen atom via F

5 treatment followed by conversion of the amide carbonyl to the
thiocarbonyl using P_2S_5 into thioamide **LIII**. The carboxylate ester can
then be hydrolyzed under standard conditions to give final compound
LIIIa (II, X = NHCS). In a similar manner, (SCHEME 2) **LIV** (from
European Patent application 661,259) can be converted to its corresponding
10 triflate **LV**. The side chain can be installed as described to give **LVI**, which
can be hydrolyzed to final product **LVIa** (II, X = *trans* -CH=CH).

SCHEME 3-4

(II, where X = $C\equiv C$, *cis* -CH=CH, or SCO)

15 Alkyne **LVII** (from European Patent application 661,259) can be
converted to its vinyl triflate **LVIII** and the side chain can be appended as
above to give **LIX**, which can be hydrolyzed directly under standard
conditions to give **LIXa** (II, X = $C\equiv C$) or hydrogenated using a weakly active
catalyst (for example, Pd/BaSO₄) to give **LX**, which can also be hydrolyzed
20 under standard conditions to give **LXa** (II, X = *cis*-CH=CH). Similarly
(SCHEME 4) (where protecting group R¹⁴ is t-butyl), thioester **LXI** (from
European Patent application 661,259) can be converted to vinyl triflate
LXII, the side chain can be installed to give **LXIII**, and the carboxylate ester
can be selectively hydrolyzed to give **LXIIIa**. (II, X = SCO).

5 **SCHEME 5**

(II, where $X = SCH_2$)

Thioether **LXIV** (from European Patent application 661,259) is converted as above into vinyl triflate **LXV** and into **LXVI** from which final compound **LXVIa** (II, $X = SCH_2$) is obtained by hydrolysis.

10

SCHEME 6

(II, where $X = OCO$ OR OCH_2)

Keto-ether **LXVII** (from European Patent application 661,259, where R^{15} is a trialkyl silyl protecting group) is converted to vinyl triflate **LXVIII**
15 as described above. The side chain is then installed as described above to give **LXIX**. Protecting group R^{15} is then selectively removed and **LXIX** ($R^{15}=H$) is acylated with commercially available methyl p-chloroformyl benzoate to give **LXX** ($R^{14} = CH_3$) which is then hydrolyzed to give **LXXa** (II, $X = OCO$). Alternatively, the protecting group can be removed from
20 **LXIX** and the freed hydroxyl alkylated with commercially available alkyl p(bromomethyl)benzoates to give **LXXI**, which can then be hydrolyzed to give **LXXIa** (II, $X = OCH_2$).

SCHEME 725 (II, where $X = NHCH_2$)

Nitrotetralone **LXXII** (from European Patent application 661,259) can be converted to vinyl triflate **LXXIII**, the side chain installed as described to give **LXXIV**, then the nitro group can be reduced to give

- 5 amino compound LXXV. Reductive amination with commercially available alkyl p-formyl benzoates will give LXXVI, which can be hydrolyzed to give final compound LXXVIa (II, X = NHCH₂).

SCHEME 8

- 10 (II, where X = COS or COO)

Keto ester LXXVII (from European Patent application 661,259) is converted into its vinyl triflate LXXVIII and then to LXXIX as described. The ester is then hydrolyzed to give LXXX, which can be reacted with alkyl p-mercaptobenzoates to give LXXXI followed by hydrolysis to give LXXXIa

- 15 (II, X = COS). Alternatively, LXXX can be reacted with alkyl p-hydroxybenzoates to give LXXXII, which can then be hydrolyzed to give LXXXIIa (II, X = COO).

SCHEME 9

- 20 (II, where X = CH₂NH, CH₂S, or CH₂O)

Ester LXXIX (from scheme 8) is reduced, using methods known in the art, to aldehyde LXXXIII. This can be reductively aminated using alkyl p-aminobenzoates to give LXXXIV, which can then be hydrolyzed to give LXXXIVa (II, X = CH₂NH). Alternatively, LXXXIII can be further reduced

- 25 to alcohol LXXXV, which can be converted using standard methods to LXXXVI (where X = Br, for example, using triphenyl phosphine and CBr₄). LXXXVI can then be used to alkylate alkyl p-mercaptobenzoates to give LXXXVII which are then hydrolyzed to give LXXXVIIa (II, X = CH₂S) or

- 5 alkylate alkyl p-hydroxybenzoates to give LXXXVIII, which can then be hydrolyzed to give LXXXVIIIa (II, X = CH₂O).

SCHEME 10

(II, where X = CR⁶=CR⁵ or COCH₂)

- 10 Acid LXXX (from scheme 8) is treated with an alkyl lithium to give LXXXIX, which is then reacted via the well-known Horner-Emmons reaction with a p-(carboalkoxy)benzyl phosphonate to give XC, which is hydrolyzed to give XCa (II, X = CR⁶=CR⁵). Intermediate ketone LXXXIX (where R⁶=CH₃) can be converted with base and chlorotrimethylsilane
- 15 into silyl enol XCI, which is then coupled under Heck conditions with commercially available alkyl p-bromobenzoates to give XCII, which can then be hydrolyzed to give XCIIa (II, X = COCH₂).

SCHEME 11

- 20 (II, where X = CONH or CSNH)

- Acid LXXX (from scheme 8) can be coupled under standard conditions (for example, by conversion to its acid chloride and coupling directly or using the free acid plus a carbodiimide activating/dehydrating agent) with alkyl p-aminobenzoates to give XCIII, which can be directly
- 25 hydrolyzed to give XCIIIa (II, X = CONH). Alternatively, XCIII can be treated with P₂S₅ to give thioamide XCIV, which can then be hydrolyzed to give XCIVa (II, X = CSNH).

5

DESCRIPTION OF SPECIFIC EMBODIMENTS

The specific examples which follow illustrate the synthesis of representative compounds of the present invention and are not to be construed as limiting the invention in sphere or scope. The methods may be adapted to variations in order to produce compounds embraced by this invention but not specifically disclosed. Further, variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art.

15

All temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), broad doublet (bd), broad triplet (bt), broad quartet (bq), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quarter (dq). The solvents employed for taking NMR spectra are DMSO- d_6 (perdeuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuteriochloroform) and other conventional deuterated solvents. The infrared (IR) spectral

5 description include only absorption wave numbers (cm^{-1}) having functional group identification value. All melting points were determined on a Gallenkamp melting point apparatus and were not corrected. Analytical grade solvents were used for reactions and chromatographies. Flash column chromatographies were performed on
10 Merck silica gel 60 (230-400 Mesh) and Merck silica gel 60 F₂₅₄ 0.5 mm plates were used.

CELITE is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

15

The abbreviations used herein are conventional abbreviations widely employed in the art.

EXAMPLE 1

20

4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-[(E)-phenylethenyl]-2-naphthalenyl]-ethenyl]benzoic acid

25

Methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-trifluoromethanesulfonyloxy-2-naphthalenyl]ethenyl]benzoate

30

A solution of methyl 4-[(E)-(5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo)-2-naphthalenyl]vinyl]benzoate (10.02 g, 30 mmol) in tetrahydrofuran (200 mL) at -78°C was treated dropwise with a solution of lithium
30 bis(trimethylsilyl)amide (1.0M in tetrahydrofuran, 42 mL, 42 mmol). The solution was stirred for 30 minutes then treated with a solution of 2-[N,N-bis(trifluoromethyl-sulfonyl)amino]pyridine (14 g, 39 mmol) in tetrahydrofuran (100 mL). The mixture was stirred overnight and was allowed to reach room temperature. The mixture was cooled down to 0-
35 5°C, diluted with water (200 mL) and ethyl acetate (200 mL). The organic

-62-

5 phase was separated and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (toluene to toluene/ethyl acetate 8:2) and triturated in hexanes to give the title
10 material (10.5 g, 75%) as a white solid.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.34 (6H, s, 2 x -CH₃), 2.45 (2H, d, J=4.8 Hz, H-6'), 3.94 (3H, s, -OCH₃), 6.02 (1H, t, J=4.8 Hz, H-7'), 7.13 (1H, d, J=16.3 Hz, vinyl H), 7.22 (1H, d, J=16.3 Hz, vinyl H), 7.34 (1H, d, J=8.0 Hz, H-4'),
15 7.51 (1H, dd, J=8.0 and 1.6 Hz, H-3'), 7.54 (1H, br s, H-1'), 7.59 (2H, d, J=8.3 Hz, H-3 and H-5), 8.05 (2H, d, J=8.4 Hz, H-2 and H-6).

Methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-[(E)-phenylethenyl]-2-naphthalenyl]ethenyl]benzoate
20

A solution of methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-trifluoromethanesulfonyloxy-2-naphthalenyl]ethenyl]benzoate (0.300 g, 0.644 mmol) in dioxane (10 mL) was treated with (E)-β-styryltributyltin (0.507 g, 25 1.29 mmol), lithium chloride (0.082 g, 1.931 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.037 g, 0.032 mmol). The solution was degassed, then heated to 95°C for ≈ 8 hours. After dilution with dichloromethane, the mixture was treated with ammonium hydroxide 10% and filtered through a celite pad. The aqueous phase was
30 then separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (hexane/ethyl acetate 19:1 to 9:1) and the solid obtained (0.261 g, 96%) was recrystallized from dichloromethane/hexane to give the title material (0.228 g, 84%) as white
35 crystals.

5 m.p.: 125°C.

IR (KBr) ν_{\max} (cm⁻¹): 2950, 1705 (C=O), 1600.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.33 (6H, s, 2 x -CH₃), 2.34 (2H, d, J=4.5 Hz, H-6'), 3.93 (3H, s, -OMe), 6.28 (1H, t, J=4.6 Hz, H-7'), 6.94 (1H, d, J=16.0 Hz, vinyl H), 7.10 (1H, d, J=16.3 Hz, vinyl H), 7.11 (1H, d, J=16.0 Hz, vinyl H), 7.23 (1H, d, J=16.3 Hz, vinyl H), 7.29-7.58 (10H, 3 sets of m, H-phenyl, H-1', H-3', H-4', H-3 and H-5), 8.02 (2H, d, J=8.4 Hz, H-2 and H-6).

Anal. Calcd. for C₃₀H₂₈O₂ · 0.5 H₂O: C 84.99; H 6.66

Found: C 84.78; H 6.65

15 4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-[(E)-phenylethenyl]-2-naphthalenyl]ethenyl]benzoic acid

To a stirred solution of methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-[(E)-phenylethenyl]-2-naphthalenyl]ethenyl]benzoate (0.206 g, 0.49 mmol) in a mixture of tetrahydrofuran/ethanol (1:1, 2 mL) was added aqueous sodium hydroxide (5N, 0.98 mL, 4.90 mmol). The mixture was stirred overnight. Hydrochloric acid 1N was then added to precipitate the acid and \approx half of the volume of the solvents was evaporated. The white solid was filtered and washed with water. The solid was then dissolved in dichloromethane/ethanol, filtered and recrystallized from this mixture by evaporating the solvents. The title compound was obtained (0.149 g, 75%) as a white solid.

IR (KBr) ν_{\max} (cm⁻¹): 3200-1800 (br), 1675 (C=O), 1600.

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.26 (6H, s, 2 x -CH₃), 2.30 (2H, d, J=4.7 Hz, H-6'), 6.36 (1H, t, J=4.7 Hz, H-7'), 6.98 (1H, d, J=16.0 Hz, vinyl H), 7.26-7.41 and 7.63-7.65 (9H, 3 sets of m, H-phenyl, vinyl H, H-1' and H-4'), 7.46 (1H, d, J=16.5 Hz, vinyl H), 7.60 (1H, dd, J=8.1 and 1.5 Hz, H-3'), 7.72 (2H, d, J=8.4 Hz, H-3 and H-5), 7.91 (2H, d, J=8.4 Hz, H-2 and H-6).

Anal. Calcd. for C₂₉H₂₆O₂: C 85.68; H 6.45

35 Found: C 85.46; H 6.28

5

EXAMPLE 2

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-biphenylethynyl)-2-naphthalenyl)-ethenyl]benzoic acid10 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-biphenylethynyl)-2-naphthalenyl)-ethenyl]benzoate

A solution of methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-trifluoromethane-sulfonyloxy-2-naphthalenyl]ethenyl]benzoate (0.400 g, 0.86 mmol) in
15 tetrahydrofuran (13 mL) was degassed and cooled down to 0-5°C. 4-Biphenylacetylene (0.382 mg, 2.15 mmol) was added in this solution, followed by bis(triphenylphosphine)palladium(II) chloride (26 mg), copper(I) iodide (26 mg) and diisopropylamine (2.1 mL). The mixture was stirred for 1 hour at 0-5°C. The resulting black solution was diluted in
20 ethyl ether, washed with water, saturated bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/toluene 0:100 to 100:0) and afforded the title compound (0.373 g, 88%) as a white solid after trituration in hexane.

25 IR (KBr) ν_{\max} (cm⁻¹): 2950, 1715 (C=O), 1605.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.34 (6H, s, 2 x -CH₃), 2.42 (2H, d, J=4.9 Hz, H-6'), 3.94 (3H, s, -OCH₃), 6.57 (1H, t, J=4.8 Hz, H-7'), 7.16 (1H, d, J=16.3 Hz, vinyl H), 7.28 (1H, d, J=16.3 Hz, vinyl H), 7.35-7.41, 7.46-7.50 and 7.63-7.69 (11H, 3 sets of m, H-3', H-4', H-biphenyl), 7.59 (2H, d, J=8.4 Hz, H-3 and
30 H-5), 7.89 (1H, d, J=1.6 Hz, H-1'), 8.04 (2H, d, J=8.3 Hz, H-2 and H-6).

Anal. Calcd. for C₃₆H₃₀O₂: C 87.42; H 6.11.

Found: C 87.37; H 6.19.

35

5 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-biphenylethynyl)-2-naphthalenyl)-
ethenyl]benzoic acid

A solution of methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-biphenylethynyl)-2-naphthalenyl)ethenyl]benzoate (0.373 g, 0.75 mmol) in tetrahydrofuran/ethanol (1:1, 12 mL) was treated with aqueous sodium hydroxide (10N, 0.75 mL) and the mixture was stirred for 18 hours at room temperature. Hydrochloric acid 1N (30 mL) was then added to precipitate the acid and the white precipitate was allowed to rest at 5°C for 1 hour. The precipitate was filtered and washed with water. The solid was then dissolved in dichloromethane/ethanol (1:1), filtered and recrystallized from this mixture by slowly evaporating the solvents. The title compound was obtained (0.290 g, 80%) as a white solid.

IR (KBr) ν_{\max} (cm⁻¹): 3650-2700 (br), 2960, 1685 (C=O), 1605.

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.38 (6H, s, 2 x -CH₃), 2.40 (2H, d, J=4.8 Hz, H-6'), 6.62 (1H, t, J=4.8 Hz, H-7'), 7.30 (1H, d, J=16.4 Hz, vinyl H), 7.41-7.44, 7.48-7.54 and 7.75-7.79 (13H, 3 sets of m, vinyl H, H-3, H-5, H-4', H-biphenyl), 7.67 (1H, br d, J=8.1 Hz, H-3'), 7.30 (1H, d, J=1.5 Hz, H-1'), 7.93 (2H, d, J=8.3 Hz, H-2 and H-6).

Anal. Calcd. for $C_{35}H_{28}O_2$: C 87.47; H 5.87.

25 Found: C 87.38; H 5.92.

5

EXAMPLE 3

4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-(4-biphenyl)-2-naphthalenyl]ethenyl]benzoic acid

The title material was prepared by the procedure described in Example 1 in
10 using 4-biphenyltrimethyltin.

Methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-(4-biphenyl)-2-naphthalenyl]ethenyl]benzoate

15 IR (KBr) ν_{\max} (cm⁻¹): 3010, 2950, 1710 (C=O), 1600.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.37 (6H, s, 2 x -CH₃), 2.40 (2H, d, J=4.7 Hz, H-6'), 3.92 (3H, s, -OCH₃), 6.1 (1H, t, J=4.7 Hz, H-7'), 6.98 (1H, d, J=16.3 Hz, vinyl-H), 7.13 (1H, d, J=16.3 Hz, vinyl-H), 7.28 (1H, d, J=1.7 Hz, H-1'), 7.39-7.52 and 7.67-7.71 (13H, 2 sets of m, H-3, H-5, H-3', H-4' and H-
20 biphenyl), 7.98 (2H, d, J=8.4 Hz, H-2 and H-6).

Anal. Calcd. for C₃₄H₃₀O₂ : C 86.78; H 6.43.

Found: C 86.85; H 6.45.

25 4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-(4-biphenyl)-2-naphthalenyl]ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3300-2000 (br), 1675 (C=O), 1600.

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.32 (6H, s, 2 x -CH₃), 2.36 (2H, d, J=4.6 Hz, H-6'), 6.10 (1H, t, J=4.6 Hz, H-7'), 7.11 (1H, d, J=16.4 Hz, vinyl H), 7.17 (1H, d, J=1.6 Hz, H-1'), 7.33 (1H, d, J=16.4 Hz, vinyl H), 7.37-7.52, 7.74-7.77 (10H, 2 sets of m, H-4', H-biphenyl), 7.63 (1H, d, J=8.1 Hz, H-3'), 7.67 (2H, d, J=8.4 Hz, H-3, H-5), 7.86 (2H, d, J=8.4 Hz, H-2, H-6).

Anal. Calcd. for C₃₃H₂₈O₂ : C 86.81; H 6.18.

35 Found: C 86.74; H 6.16.

5

EXAMPLE 4

4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-(3-biphenyl)-2-naphthalenyl]ethenyl]benzoic acid

10

The title material was prepared by the procedure described in Example 1 in using 3-biphenyltrimethyltin.

Methyl 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-(3-biphenyl)-2-naphthalenyl]ethenyl]benzoate

15

IR (KBr) ν_{\max} (cm⁻¹): 3100, 2950, 2910, 1710 (C=O), 1600.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.39 (6H, s, 2 x -CH₃), 2.41 (2H, d, J=4.7 Hz, H-6'), 3.91 (3H, s, -OCH₃), 6.10 (1H, t, J=4.7 Hz, H-7'), 6.97 (1H, d, J=16.3 Hz, vinyl-H), 7.12 (1H, d, J=16.3 Hz, vinyl-H), 7.25 (1H, d, J=1.7 Hz, H-1'), 7.36-7.40, 7.42-7.53 and 7.61-7.68 (13H, 3 sets of m, H-3, H-5, H-3', H-4', H-biphenyl) 7.98 (2H, d, J=8.5 Hz, H-2 and H-6).

20

Anal. Calcd. for C₃₄H₃₀O₂: C 86.78; H 6.43.

Found: C 87.44; H 6.41.

25

4-[(E)-[5,6-Dihydro-5,5-dimethyl-8-(3-biphenyl)-2-naphthalenyl]ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3700-2000 (br), 1680 (C=O), 1600.

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.33 (6H, s, 2 x -CH₃), 2.36 (2H, d, J=4.6 Hz, H-6'), 6.14 (1H, t, J=4.6 Hz, H-7'), 7.09 (1H, d, J=16.4 Hz, vinyl H), 7.16 (1H, d, J=0.9 Hz, H-biphenyl), 7.29-7.39, 7.44-7.49, 7.63-7.72 (12H, 3 sets of m, vinyl H, H-3', H-4', H-biphenyl, H-3 and H-5), 7.61 (1H, d, J=1.6 Hz, H-1'), 7.86 (2H, d, J=8.3 Hz, H-2 and H-6).

30

35 Anal. Calcd. for C₃₃H₂₈O₂ · 0.55 H₂O: C 84.97; H 6.29.

5

Found: C 84.94; H 6.25.

EXAMPLE 5

10 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-phenylethynyl-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared by the procedure described in Example 1 in using 8-phenylethynyltributyltin.

15

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-phenylethynyl-2-naphthalenyl)-ethenyl]benzoate

IR (KBr) ν_{\max} (cm⁻¹): 2960, 1715 (C=O), 1600.

20 ¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.33 (6H, s, 2 x -CH₃), 2.40 (2H, d, J=4.9 Hz, H-6'), 3.94 (3H, s, -OCH₃), 6.55 (1H, t, J=4.9 Hz, H-7'), 7.15 (1H, d, J=16.3 Hz, vinyl H), 7.27 (1H, d, J=16.3 Hz, vinyl H), 7.30-7.43 (4H, m, H-3, H-5, H-4' and H-phenyl), 7.48 (1H, dd, J=8.0 and 1.8 Hz, H-3'), 7.58-7.62 (4H, m, H-phenyl), 7.87 (1H, d, J=1.7 Hz, H-1'), 8.03 (2H, d, J=8.3 Hz, H-2 and H-6).

25 Anal. Calcd. for C₃₀H₂₆O₂: C 86.09; H 6.26.

Found: C 85.88; H 5.90.

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-phenylethynyl-2-naphthalenyl)ethenyl]benzoic acid

30

IR (KBr) ν_{\max} (cm⁻¹): 2960, 1715 (C=O), 1600.

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.27 (6H, s, 2 x -CH₃), 2.38 (2H, d, J=4.8 Hz, H-6'), 6.60 (1H, t, J=4.8 Hz, H-7'), 7.29 (1H, d, J=16.4 Hz, vinyl H), 7.40-7.48 and 7.63-7.67 (7H, 2 sets of m, H-3', H-4' and H-phenyl), 7.50 (1H,

- 5 d, J=16.4 Hz, vinyl H), 7.76 (2H, d, J=8.3 Hz, H-3 and H-5), 7.77 (1H, s, H-1'),
7.93 (2H, d, J=8.3 Hz, H-2 and H-6), 12.86 (1H, br s, COOH).

Anal. Calcd. for $C_{29}H_{24}O_2$: C 86.11; H 5.98.

Found: C 85.81; H 5.73.

10

EXAMPLE 6

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-[(Z)-phenylethenyl]-2-naphthalenyl)ethenyl]-benzoic acid

- 15 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-[(Z)-phenylethenyl]-2-naphthalenyl)-ethenyl]benzoate

- A stirred solution of methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-phenylethynyl-2-naphthalenyl)ethenyl]benzoate (0.317 g, 0.76 mmol) in
20 pyridine (10 mL) was treated with 10% palladium on barium sulfate and hydrogenated. The mixture was stirred at room temperature for 4 hours, then filtered. The residue was concentrated, diluted with ethyl acetate, washed with 1N hydrochloric acid, saturated sodium bicarbonate and
25 brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (toluene) to give a solid which was triturated in hexane (0.208 g, 65%).

IR (KBr) ν_{\max} (cm⁻¹): 2965, 1715 (C=O), 1600, 1275.

- 30 ¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.31 (6H, s, 2 x -CH₃), 2.22 (2H, dd, J=4.5 and 2.2 Hz, H-6'), 3.93 (3H, s, -OCH₃), 5.93 (1H, td, J=4.5 and 1.5 Hz, H-7'), 6.43 (1H, dqa, J=12.0 and 1.9 Hz, vinyl-H-1''), 6.72 (1H, d, J=12.0 Hz, vinyl-H-2''), 7.03 (1H, d, J=16.2 Hz, vinyl H), 7.12-7.22 and 7.35-7.43 (2 x 4H, 2 sets of m, H-3', H-4', vinyl-H, phenyl), 7.48 (1H, d, J=1.4 Hz, H-1'), 7.55 (2H, d,
35 J=8.3 Hz, H-3 and H-5), 8.02 (2H, d, J=8.4 Hz, H-2 and H-6).

5

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-[(Z)-phenylethenyl]-2-naphthalenyl)-ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3600-2700 (br), 1680 (C=O), 1600, 1420, 1290.

- 10 ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.26 (6H, s, 2 x -CH₃), 2.19 (2H, dd, J=4.1 and 1.9 Hz, H-6'), 5.87 (1H, br t, J=4.1 Hz, H-7'), 6.49 (1H, dd, J=12.1 and 1.8 Hz, vinyl-H-1"), 6.74 (1H, d, J=12.1 Hz, vinyl-H-2"), 7.12-7.28 and 7.31-7.40 (8H, 2 sets of m, H-3', vinyl H, phenyl), 7.43 (1H, d, J=1.4 Hz, H-1'), 7.53 (1H, d, J=8.0 Hz, H-4'), 7.69 (2H, d, J=8.3 Hz, H-3 and H-5), 7.91 (2H, d, J=8.4
- 15 Hz, H-2 and H-6).

Anal. Calcd. for C₂₉H₂₆O₂: C 85.68; H 6.45.

Found: C 85.04; H 6.19.

EXAMPLE 7

20

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-phenylethynyl)-2-naphthalenyl]ethynyl]benzoic acid

- The title material was prepared by the procedure described in Example 1 by
- 25 using 8-phenylethynyltributyltin and 4-[(E)-[5,6-dihydro-5,5-dimethyl-8-trifluoro-methanesulfonyloxy-2-naphthalenyl]ethynyl]benzoate.

Ethyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-phenylethynyl)-2-naphthalenyl]ethynyl]benzoate

30

IR (KBr) ν_{\max} (cm⁻¹): 2990, 1715 (C=O), 1605, 1275.

¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.33 (6H, s, 2 x -CH₃), 1.42 (3H, t, J=7.1 Hz, -OCH₂CH₃), 2.40 (2H, d, J=4.8 Hz, H-6'), 4.40 (2H, qa, J=7.1 Hz, -OCH₂-), 7.33 (1H, d, J=8.0 Hz, H-4'), 7.32-7.40 (4H, m, phenyl), 7.46 (1H, dd, J=8.0 and

-71-

- 5 1.6 Hz, H-3'), 7.59 (1H, dd, J=7.7 and 1.5 Hz, phenyl), 7.61 (1H, d, J=8.4 Hz, H-3 and H-5), 7.87 (1H, d, J=1.5 Hz, H-1'), 8.03 (2H, d, J=8.3 Hz, H-2 and H-6).

10 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-phenylethynyl)-2-naphthalenyl]ethynyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3650-2250 (br), 1680, 1605.

- ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.27 (6H, s, 2 x -CH₃), 2.41 (2H, d, J=4.8 Hz, H-6'), 6.64 (1H, t, J=4.8 Hz, H-7'), 7.44-7.47 and 7.60-7.62 (4H and
15 2H, 2 sets of m, phenyl and H-4'), 7.55 (1H, dd, J=8.0 and 1.7 Hz, H-3'), 7.69 (2H, d, J=8.3 Hz, H-3 and H-5), 7.72 (1H, d, J=1.7 Hz, H-1'), 7.96 (2H, d, J=8.4 Hz, H-2 and H-6).

Anal. Calcd. for C₂₉H₂₂O₂ · 0.25 H₂O: C 85.58; H 5.47.

Found: C 85.55; H 5.80.

20

EXAMPLE 8

25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-methylphenylethynyl)-2-naphthalenyl)-ethenyl]benzoic acid

25

The title material was prepared by the procedure described in Example 1 by using 4-methylphenylethynyltributyltin.

30 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-methylphenylethynyl)-2-naphthalenyl)ethenyl]benzoate

IR (KBr) ν_{\max} (cm⁻¹): 2950, 1715 (C=O), 1605.

- ¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.33 (6H, s, 2 x -CH₃), 2.40 (2H, d
overlapped by -CH₃, H-6'), 2.41 (3H, s, -CH₃), 3.94 (3H, s, -OCH₃), 6.52 (1H, t,
35 J=4.8 Hz, H-7'), 7.14 (1H, d, J=16.3 Hz, vinyl H), 7.26 (1H, d, J=16.3 Hz, vinyl

-72-

- 5 H), 7.12-7.28 and 7.45-7.50 (5H, 2 sets of m, H-3' and H-tolyl), 7.34 (1H, d, J=8.0 Hz, H-4'), 7.58 (2H, d, J=8.4 Hz, H-3 and H-5), 7.87 (1H, d, J=1.6 Hz, H-1'), 8.03 (2H, d, J=8.3 Hz, H-2 and H-6).

Anal. Calcd. for $C_{31}H_{28}O_2 \cdot 0.4 H_2O$: C 84.67; H 6.60.

Found: C 84.69; H 6.34.

10

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-methylphenylethynyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{max} (cm^{-1}): 3650-2300 (br), 2960, 1670 (C=O), 1605.

- 15 1H NMR 400 MHz (DMSO- d_6) δ (ppm): 1.26 (6H, s, 2 x -CH₃), 2.36 (3H, s, -CH₃), 2.37 (2H, d overlapped by -CH₃, H-6'), 6.56 (1H, t, J=4.8 Hz, H-7'), 7.26-7.30 and 7.48-7.55 (6H, 2 sets of m, vinyl H, H-tolyl), 7.41 (1H, d, J=8.1 Hz, H-4'), 7.66 (1H, d, J=8.1 Hz, H-3'), 7.75 (2H, d, J=8.3 Hz, H-3 and H-5), 7.76 (1H, s, H-1'), 7.93 (2H, d, J=8.3 Hz, H-2 and H-6).

- 20 Anal. Calcd. for $C_{30}H_{26}O_2 \cdot 0.5 H_2O$: C 84.28; H 6.37.

Found: C 84.38; H 6.34.

EXAMPLE 9

- 25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-fluorophenylethynyl)-2-naphthalenyl)-ethenyl]benzoic acid

The title material was prepared by the procedure described in Example 1 by using 4-fluorophenylethynyltributyltin.

30

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-fluorophenylethynyl)-2-naphthalenyl)ethenyl]benzoate

IR (KBr) ν_{max} (cm^{-1}): 2950, 1710 (C=O), 1605.

-73-

- 5 ^1H NMR 400 MHz (CDCl_3) δ (ppm): 1.33 (6H, s, 2 x $-\text{CH}_3$), 2.40 (2H, d, $J=4.8$ Hz, H-6'), 3.94 (3H, s, $-\text{OCH}_3$), 6.54 (1H, t, $J=4.8$ Hz, H-7'), 7.07-7.15 (2H, m, H-phenyl), 7.14 (1H, d, $J=16.1$ Hz, vinyl H), 7.23-7.27 (1H, d overlapped by CDCl_3 , vinyl H), 7.35 (1H, d, $J=8.0$ Hz, H-4'), 7.48 (1H, dd, $J=8.0$ and 1.5 Hz, H-3'), 7.55-7.59 (2H, m, H-phenyl), 7.58 (2H, d, $J=8.3$ Hz, H-3 and H-5), 7.82
- 10 (1H, d, $J=1.5$ Hz, H-1'), 8.03 (2H, d, $J=8.4$ Hz, H-2 and H-6).

Anal. Calcd. for $\text{C}_{30}\text{H}_{25}\text{O}_2\text{F}$: C 82.54; H 5.77; F 4.35.

Found: C 82.20; H 5.84; F 4.15.

- 15 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-fluorophenylethynyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{max} (cm^{-1}): 3650-2300 (br), 2950, 1660 ($\text{C}=\text{O}$), 1600.

- ^1H NMR 400 MHz ($\text{DMSO}-d_6$) δ (ppm): 1.26 (6H, s, 2 x $-\text{CH}_3$), 2.38 (2H, d, $J=4.7$ Hz, H-6'), 6.59 (1H, t, $J=4.7$ Hz, H-7'), 7.28 (1H, d, $J=16.3$ Hz, vinyl H), 7.27-7.33 (2H, m, H-phenyl), 7.41 (1H, d, $J=8.0$ Hz, H-4'), 7.50 (1H, d, $J=16.3$ Hz, vinyl H), 7.66 (1H, d, $J=8.0$ Hz, H-3'), 7.70-7.76 (3H, m, H-1' and H-phenyl), 7.75 (2H, d, $J=8.2$ Hz, H-3 and H-5), 7.93 (2H, d, $J=8.2$ Hz, H-2 and H-6).
- 20

25

Anal. Calcd. for $\text{C}_{29}\text{H}_{23}\text{O}_2\text{F} \cdot 0.1 \text{H}_2\text{O}$: C 82.09; H 5.51.

Found: C 82.1; H 5.6.

EXAMPLE 10

30

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(3-pyridinyl-ethynyl)-2-naphthalenyl)-ethenyl]benzoic acid

- The title material was prepared by the procedure described in Example 1
- 35 using tributyl(3-pyridinylethynyl)tin.

5

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(3-pyridinyl-ethynyl)-2-naphthalenyl)ethenyl]benzoate

IR (KBr) ν_{\max} (cm⁻¹): 3100-2800 (w, aromatic, aliphatic), 1715 (s, C=O), 1600 (s, C=C).

10

¹H NMR 400 MHz (CDCl₃) δ (ppm): 8.83 (d, J=1.7 Hz, 1H, H-2 in pyridyl), 8.58 (dd, J=4.8, 1.4 Hz, 1H, H-6 in pyridyl), 8.02 (d, J=8.3 Hz, 2H, H-2, H-6), 7.85 (ddd, J=7.8, 1.9, 1.9 Hz, 1H, H-4 in pyridyl), 7.80 (d, J=1.5 Hz, 1H, H-1'), 7.57 (d, J=8.3 Hz, 2H, H-3, H-5), 7.48 (dd, J=8.0, 1.6 Hz, 1H, H-3'), 7.35 (d, J=8.2 Hz, 1H, H-4'), 7.32 (dd, J=7.9, 3.0 Hz, 1H, H-5 in pyridyl), 7.24 (d, J=16.3 Hz, 1H, vinyl H), 7.12 (d, J=16.3 Hz, 1H, vinyl H), 6.59 (t, J=4.8 Hz, 1H, H-7'), 3.92 (s, 3H, CO₂CH₃), 2.40 (d, J=4.8 Hz, 2H, H-6'), 1.56 (s, 6H, 2 x CH₃).

15

20

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(3-pyridinyl-ethynyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3600-2100 (br, s, CO₂H, aromatic, aliphatic), 2220 (w, acetylene), 1690 (s, C=O), 1605 (s, C=C).

25

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 8.86 (s, 1H, H-2 in pyridyl), 8.60 (dd, J=4.9, 1.5 Hz, 1H, H-6 in pyridyl), 8.06 (d, J=8.0 Hz, 1H, H-4 in pyridyl), 7.92 (d, J=8.3 Hz, 2H, H-2, H-6), 7.77 (d, J=1.5 Hz, 1H, H-1'), 7.75 (d, J=8.3 Hz, 2H, H-3, H-5), 7.67 (d, J=8.1 Hz, 1H, H-3'), 7.51 (d, J=16.8 Hz, 1H, vinyl H), 7.49 (dd, J=7.3, 7.3 Hz, 1H, H-5 in pyridyl), 7.41 (d, J=8.1 Hz, 1H, H-4'), 7.30 (d, J=16.5 Hz, 1H, vinyl H), 6.65 (t, J=4.8 Hz, 1H, H-7'), 2.39 (d, J=4.9 Hz, 2H, H-6'), 1.26 (s, 6H, 2 x CH₃).

30

Anal. Calcd for C₂₈H₂₃NO₂·0.5 H₂O: C, 81.13; H, 5.84; N, 3.38.

Found: C, 81.21; H, 5.93; N, 3.32.

35

5

EXAMPLE 11

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-(imidazol-1-yl)phenyl)-2-naphthalenyl)ethenyl]benzoic acid

10 The title material was prepared as described in Example 1 using tributyl-(4-(imidazol-1-yl)phenyl)tin.

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-(imidazol-1-yl)phenyl)-2-naphthalenyl)ethenyl]benzoate

15

IR (KBr) ν_{\max} (cm^{-1}): 3100-2800(w, aromatic, aliphatic), 1700 (s, C=O), 1600 (s, C=C).

^1H NMR 400 MHz (CDCl_3) δ (ppm): 7.97 (d, $J=8.3$ Hz, 2H, H-2, H-6), 7.94 (s, 1H, H-2 in imidazole), 7.51-7.40 (m, 8H, H-5, H-3, H-4'-H-3', phenyl in 8'),
20 7.36 (s, 1H, H-4 or H-5 in imidazole), 7.25 (s, 1H, H-4 or H-5 in imidazole), 7.13 (d, $J=1.5$ Hz, 1H, H-1'), 7.10 (d, $J=16.4$ Hz, 1H, vinyl H), 6.95 (d, $J=16.3$ Hz, 1H, vinyl H), 6.07 (t, $J=4.6$ Hz, 1H, H-7'), 3.90 (s, 3H, CO_2CH_3), 2.39 (d, $J=4.7$ Hz, 2H, H-6'), 1.37 (s, 6H, 2 x CH_3).

25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-(imidazol-1-yl)phenyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm^{-1}): 3700-2200 (br, s, CO_2H , HCl, aromatic, aliphatic), 1680 (s, C=O), 1605 (s, C=C).

30 ^1H NMR 400 MHz ($\text{DMSO}-d_6$) δ (ppm): 8.26 (s, 1H, H-2 in imidazole), 7.86 (d, $J=8.2$ Hz, 2H, H-2, H-6), 7.85 (two sets of doublets, 4H), 7.79 (s, 1H, H-5 or H-4 in imidazole), 7.61 (two sets of doublets, 4H), 7.61 (s, 1H, H-5 or H-4 in imidazole), 7.29 (d, $J=16.5$ Hz, 1H, vinyl H), 7.09 (d, $J=16.4$ Hz, 1H, vinyl H), 7.09 (s, 1H, H-1'), 6.13 (t, $J=4.5$ Hz, 1H, H-7'), 2.36 (d, $J=4.5$ Hz, 2H, H-6'), 1.31
35 (s, 6H, 2 x CH_3).

5 Anal. Calcd for C₃₀H₂₆N₂O₂.2.8 H₂O.HCl: C, 67.55; H, 6.16; N, 5.25.
 Found: C, 67.53; H, 6.08; N, 4.91.

EXAMPLE 12

10 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-(2-formyl) thiophenyl)-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(4-(2-formyl)thiophenyl)tin.

15

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-(2-formyl) thiophenyl)-2-naphthalenyl)ethenyl]benzoate

IR (KBr) ν_{max} (cm⁻¹): 3100-2800 (w, aromatic, aliphatic), 1715 (s, C=O), 1680 (s, C=O), 1600 (s, C=C).

20

¹H NMR 400 MHz (CDCl₃) δ (ppm): 9.96 (s, 1H, CHO), 7.99 (d, J=8.3 Hz, 2H, H-2, H-6), 7.81 (s, 1H, H-3 in thiophene), 7.70 (s, 1H, H-5 in thiophene), 7.51 (d, J=8.3 Hz, 2H, H-3, H-5), 7.47 (dd, J=7.9, 1.2 Hz, 1H, H-3'), 7.40 (d, J=8.0 Hz, 1H, H-4'), 7.19 (d, J=1.2 Hz, 1H, H-1'), 7.12 (d, J=16.4 Hz, 1H, vinyl H), 6.98 (d, J=16.3 Hz, 1H, vinyl H), 6.14 (t, J=4.7 Hz, 1H, H-7'), 3.91 (s, 3H, CO₂CH₃), 2.36 (d, J=4.7 Hz, 2H, H-6'), 1.34 (s, 6H, 2 x CH₃).

25

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-(2-formyl) thiophenyl)-2-naphthalenyl)ethenyl]benzoic acid

30

IR (KBr) ν_{max} (cm⁻¹): 3700-2200(br, s, CO₂H, aromatic, aliphatic), 1680 (s, C=O, aldehyde and ester), 1600 (s, C=C).

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 9.98 (s, 1H, CHO), 8.11 (d, J=8.5 Hz, 2H, H-2, H-6), 7.90 (s, 1H, H-3 or H-5 in thiophene); 7.88 (s, 1H, H-3 or H-5 in thiophene), 7.68 (d, J=8.2 Hz, 2H, H-3, H-5), 7.64 (d, J=8.0 Hz, 1H, H-4' or

35

-77-

- 5 H-3'), 7.44 (d, J=8.0 Hz, 1H, H-4' or H-3'), 7.37 (d, J=16.5 Hz, 1H, vinyl H), 7.25 (s, 1H, H-1'), 7.16 (d, J=16.5 Hz, 1H, vinyl H), 6.23 (t, J=4.8 Hz, 1H, H-7'), 2.33 (d, J=4.7 Hz, 2H, H-6'), 1.29 (s, 6H, 2 x CH₃).

Anal. Calcd for C₂₆H₂₂O₃S.0.6 H₂O: C, 73.42; H, 5.50.

Found: C, 73.76; H, 5.67.

10

EXAMPLE 13

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-methoxy-pyridinyl))-2-naphthalenyl)ethenyl]benzoic acid

15

The title material was prepared as described in Example 1 using tributyl(5-(2-methoxy-pyridyl)tin.

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(5-(2-methoxy-pyridinyl))-2-naphthalenyl)ethenyl]benzoate

20

- ¹H NMR 400 MHz (CDCl₃) δ (ppm): 8.19 (s, 1H, H-6 in pyridyl), 7.99 (d, J=8.3 Hz, 2H, H-2, H-6), 7.59 - 7.38 (m, 3H, H-3 and H-4 in pyridyl and H-3), 7.51 (d, J=8.3 Hz, 2H, H-3, H-5), 7.10 (d, J=16.2 Hz, 1H, vinyl H), 7.10 (s, 1H, H-1'), 25 6.95 (d, J=16.3 Hz, 1H, vinyl H), 6.81 (d, J=8.4 Hz, 1H, H-4'), 6.01 (t, J=4.6 Hz, 1H, H-7'), 4.01 (s, 3H, OCH₃), 3.92 (s, 3H, CO₂CH₃), 2.38 (d, J=4.6 Hz, 2H, H-6'), 1.36 (s, 6H, 2 x CH₃).

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-methoxy-pyridinyl))-2-naphthalenyl)ethenyl]benzoic acid

30

IR (KBr) ν_{max} (cm⁻¹): 3600-2300(br, s, CO₂H, aromatic, aliphatic), 1675 (s, C=O), 1600 (s, C=C).

- ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 8.14 (s, 1H, H-5 in pyridyl), 7.87 (d, 35 J=7.2 Hz, 2H, H-2, H-6), 7.69 (d, J=9.8 Hz, 2H, H-3, H-5), 7.66 (m, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.43 (d, J=7.7 Hz, 1H), 7.32 (d, J=16.4 Hz, 1H, vinyl H), 7.11 (d,

-78-

- 5 J=16.4 Hz, 1H, vinyl H), 7.04 (s, 1H, H-1'), 6.88 (d, J=7.7 Hz, 1H), 6.04 (t, J=4.5 Hz, 1H, H-7'), 3.90 (s, 3H, OCH₃), 2.32 (d, J=4.1 Hz, 2H, H-6'), 1.30 (s, 6H, 2 x CH₃).

Anal. Calcd for C₂₇H₂₅NO₃·0.8 H₂O: C, 76.14; H, 6.30; N, 3.29.

- 10 Found: C, 75.90; H, 6.11; N, 3.05.

EXAMPLE 14

- 15 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(indol-5-yl)-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(indol-5-yl)tin.

- 20 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(indol-5-yl)-2-naphthalenyl)ethenyl]benzoate

IR (KBr) ν_{\max} (cm⁻¹): 3400 (s, amine), 3100-2800(w, aromatic, aliphatic), 1710 (s, C=O), 1600 (s, C=C).

- 25 ¹H NMR 400 MHz (CDCl₃) δ (ppm): 8.22 (br s, 1H), 7.94 (d, J=8.2 Hz, 2H, H-2, H-6), 7.66 (s, 1H), 7.46-7.37 (m, 3H), 7.43 (d, J=8.0 Hz, 2H, H-3, H-5), 7.26-7.20 (m, 2H), 7.07 (d, J=16.3 Hz, 1H, vinyl H), 6.91 (d, J=16.3 Hz, 1H, vinyl H), 6.59 (br s, 1H), 6.03 (t, J=4.5 Hz, 1H, H-7'), 3.85 (s, 3H, CO₂CH₃), 2.38 (d, J=4.6 Hz, 2H, H-6'), 1.38 (s, 6H, 2 x CH₃).

30

- 35 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(indol-5-yl)-2-naphthalenyl)ethenyl]benzoic acid

5

IR (KBr) ν_{\max} (cm⁻¹): 3380 (m, amine), 3500-2200 (br, m, CO₂H, aromatic, aliphatic), 1685 (s, C=O), 1605 (s, C=C).

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 7.82 (d, J=8.4 Hz, 2H, H-2, H-6), 7.62 (d, J=8.4 Hz, 2H, H-3, H-5), 7.58 (dd, J=8.1, 1.6 Hz, 1H), 7.50 (s, 1H), 7.43 (d, J=5.5 Hz, 1H), 7.41 (d, J=5.2 Hz, 1H), 7.36 (dd, J=2.8, 2.8 Hz, 1H), 7.24 (d, J=16.4 Hz, 1H, vinyl H), 7.13 (d, J=1.6 Hz, 1H), 7.03 (d, J=16.7 Hz, 1H, vinyl H), 7.02 (dd, J=8.9, 1.5 Hz, 1H), 6.44 (br s, 1H), 5.96 (t, J=4.6 Hz, 1H, H-7'), 2.32 (d, J=4.6 Hz, 2H, H-6'), 1.32 (s, 6H, 2 x CH₃).

Anal. Calcd for C₂₉H₂₅NO₂·0.7 H₂O: C, 80.60; H, 6.16; N, 3.24.
 Found: C, 80.63; H, 6.37; N, 3.06.

EXAMPLE 15

20 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-dimethylamino)pyridinyl)-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(5-(2-dimethylamino)pyridinyl)tin.

25 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(5-(2-dimethylamino)pyridinyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3100-2800 (w, aromatic, aliphatic), 1710 (s, C=O), 1600 (s, C=C), 1270 (s, tertiary amine).

30 ¹H NMR 400 MHz (CDCl₃) δ (ppm): 8.21 (d, J=2.3 Hz, 1H, H-6 in pyridyl), 7.98 (d, J=8.3 Hz, 2H, H-2, H-6), 7.50 (d, J=8.4 Hz, 2H, H-3, H-5), 7.46 (dd, J=8.7, 2.4 Hz, 1H, H-4 in pyridyl), 7.43 (dd, J=8.1, 1.7 Hz, 1H, H-3'), 7.37 (d, J=8.0 Hz, 1H, H-4'), 7.19 (d, J=1.5 Hz, 1H, H-1'), 7.11 (d, J=16.3 Hz, 1H, vinyl H), 6.96 (d, J=16.3 Hz, 1H, vinyl H), 6.58 (d, J=8.7 Hz, 1H, H-3 in pyridyl),

- 5 5.96 (t, J=4.6 Hz, 1H, H-7'), 3.91 (s, 3H, CO₂CH₃), 3.15 (s, 6H, N(CH₃)₂), 2.34 (d, J=4.7 Hz, 2H, H-6'), 1.34 (s, 6H, 2 x CH₃).

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-dimethylamino)pyridinyl)-2-naphthalenyl)ethenyl]benzoic acid

10

IR (KBr) ν_{\max} (cm⁻¹): 3700-2100 (br, s, CO₂H, HCl, aromatic, aliphatic), 1680, 1655 (s, C=O), 1605 (s, C=C), 1290 (tertiary amine).

- ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 7.93 (d, J=8.0Hz, 1H, H-4 in pyridyl), 7.91 (d, J=2.0 Hz, 1H, H-6 in pyridyl), 7.89 (d, J=8.7 Hz, 2H, H-2, H-6), 7.65 (d, J=7.7 Hz, 2H, H-3, H-5), 7.61 (d, J=8.1 Hz, 1H, H-3'), 7.44 (d, J=8.0 Hz, 1H, H-4'), 7.31 (d, J=16.5 Hz, 1H, vinyl H), 7.28 (d, J=9.5 Hz, 1H, H-3 in pyridyl), 7.17 (d, J=16.4 Hz, 1H, vinyl H), 7.09 (s, 1H, H-1'), 6.14 (t, J=4.2 Hz, 1H, H-7'), 3.27 (s, 6H, N(CH₃)₂), 2.34 (d, J=4.3 Hz, 2H, H-6'), 1.30 (s, 6H, 2 x CH₃).

- Anal. Calcd for C₂₈H₂₈N₂O₂·2.0 H₂O·HCl: C, 67.66; H, 6.69; N, 5.64.
20 Found: C, 67.62; H, 6.66; N, 5.47.

EXAMPLE 16

- 25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-aminopyridinyl))-2-naphthalenyl)ethenyl]benzoic acid

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(5-(2-aminopyridinyl))-2-naphthalenyl)ethenyl]benzoate

- 30 IR (KBr) ν_{\max} (cm⁻¹): 3480 (w, amine), 3100-2800(w, aromatic, aliphatic), 1715 (s, C=O), 1600 (s, C=C), 1280 (s, amine).
¹H NMR 400 MHz (CDCl₃) δ (ppm): 8.11 (d, J=1.9 Hz, 1H, H-6 in pyridyl), 7.98 (d, J=8.4 Hz, 2H, H-2, H-6), 7.51 (d, J=8.5 Hz, 2H, H-3, H-5), 7.45 (dd, J=8.3, 2.2 Hz, 1H, H-3 in pyridyl), 7.43 (dd, J=7.2, 1.7 Hz, 1H, H-3'), 7.37 (d, J=8.0 Hz, 1H, H-4'), 7.16 (d, J=1.6 Hz, 1H, H-1'), 7.11 (d, J=16.4 Hz, 1H, vinyl
35

- 5 H), 6.96 (d, J=16.3 Hz, 1H, vinyl H), 6.57 (d, J=8.8 Hz, 1H, H-4 in pyridyl), 5.98 (t, J=4.7 Hz, 1H, H-7'), 3.91 (s, 3H, CO₂CH₃), 2.35 (d, J=4.7 Hz, 2H, H-6'), 1.29 (s, 6H, 2 x CH₃).

10 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-(2-aminopyridinyl))-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3700-2000 (br, s, CO₂H, HCl, aromatic, aliphatic, amine), 1670 (s, C=O), 1600 (s, C=C), 1280 (amine).

- ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 7.95 (s, 1H, H-6 in pyridyl), 7.91 (d, J=7.6 Hz, 2H, H-2, H-6), 7.87 (d, J=9.0 Hz, 1H, H-4 in pyridyl), 7.66 (d, J=7.9 Hz, 2H, H-3, H-5), 7.61 (d, J=8.1 Hz, 1H, H-3'), 7.43 (d, J=8.1 Hz, 1H, H-4'), 7.34 (d, J=16.5 Hz, 1H, vinyl H), 7.19 (d, J=16.4 Hz, 1H, vinyl H), 7.12 (s, 1H, H-1'), 7.02 (d, J=9.1 Hz, 1H, H-3 in pyridyl), 6.12 (t, J=4.4 Hz, 1H, H-7'), 2.32 (d, J=4.3 Hz, 2H, H-6'), 1.29 (s, 6H, 2 x CH₃).
- 20 Anal. Calcd for C₂₆H₂₄N₂O₂·0.5 H₂O·HCl: C, 70.66; H, 5.93; N, 6.34.
Found: C, 70.63; H, 5.92; N, 5.97.

EXAMPLE 17

25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(2-benzofuryl))-2-naphthalenyl]ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(2-benzofuryl)tin.

30 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(2-benzofuryl))-2-naphthalenyl]ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3100-2800(w, aromatic, aliphatic), 1715 (s, C=O), 1605 (s, C=C).

- 5 ^1H NMR 400 MHz (CDCl_3) δ (ppm): 8.00 (d, $J=8.4$ Hz, 2H, H-2, H-6), 7.69 (d, $J=1.6$ Hz, 1H), 7.62 (dd, $J=7.3, 1.0$ Hz, 1H), 7.54 (d, $J=8.3$ Hz, 2H, H-3, H-5), 7.53 (d, $J=7.6$ Hz, 1H), 7.49 (dd, $J=8.0, 1.7$ Hz, 1H), 7.41 (d, $J=8.0$ Hz, 1H), 7.31 (ddd, $J=7.2, 7.2, 1.3$ Hz, 1H, H-5 or H-6 in benzofuryl), 7.26 (ddd, $J=7.2, 7.2, 1.0$ Hz, 1H, H-5 or H-6 in benzofuryl), 7.20 (d, $J=16.3$ Hz, 1H, vinyl H), 7.05 (d, $J=16.3$ Hz, 1H, vinyl H), 6.86 (s, 1H), 6.67 (t, $J=5.0$ Hz, 1H, H-7'), 3.91 (s, 3H, CO_2CH_3), 2.41 (d, $J=5.0$ Hz, 2H, H-6'), 1.35 (s, 6H, $2 \times \text{CH}_3$).
- 10

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(2-benzofuryl)-2-naphthalenyl)ethenyl]benzoic acid

15

IR (KBr) ν_{max} (cm^{-1}): 3700-2100 (br, s, CO_2H , aromatic, aliphatic), 1680 (s, C=O), 1600 (s, C=C).

- ^1H NMR 400 MHz ($\text{DMSO}-d_6$) δ (ppm): 7.88 (d, $J=7.8$ Hz, 2H, H-2, H-6), 7.69 (d, $J=7.9$ Hz, 2H, H-3, H-5), 7.67 - 7.65 (m, 3H), 7.60 (d, $J=7.9$ Hz, 1H), 7.46 (d, $J=7.6$ Hz, 1H), 7.43 (d, $J=15.9$ Hz, 1H, vinyl H), 7.33 (dd, $J=7.3, 7.3$ Hz, 1H, H-5 or H-6 in benzofuryl), 7.27 (dd, $J=7.4, 7.4$ Hz, 1H, H-5 or H-6 in benzofuryl), 7.23 (d, $J=16.7$ Hz, 1H, vinyl H), 7.10 (s, 1H), 6.69 (t, $J=4.7$ Hz, 1H, H-7'), 2.39 (d, $J=4.8$ Hz, 2H, H-6'), 1.29 (s, 6H, $2 \times \text{CH}_3$).
- 20

Anal. Calcd for $\text{C}_{29}\text{H}_{24}\text{O}_3 \cdot 0.5 \text{H}_2\text{O}$: C, 81.10; H, 5.87.

- 25 Found: C, 80.86; H, 5.80.

EXAMPLE 18

- 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(1-naphthalenyl)-2-naphthalenyl)-ethenyl]benzoic acid
- 30

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(1-naphthalenyl)-2-naphthalenyl)ethenyl]benzoic acid

5 IR (KBr) ν_{\max} (cm⁻¹): 3100-2800(w, aromatic, aliphatic), 1715 (s, C=O), 1605 (s, C=C).

¹H NMR 400 MHz (CDCl₃) δ (ppm): 7.92 - 7.88 (m, 2H), 7.90 (d, J=8.4 Hz, 2H, H-2, H-6), 7.76 (d, J=8.4 Hz, 1H), 7.54 (dd, J=7.1, 7.1 Hz, 1H), 7.48 - 7.41 (m, 4H), 7.36 (d, J=8.3 Hz, 2H, H-3, H-5), 7.33 (m, 1H), 6.89 (d, J=16.3 Hz, 1H, vinyl H), 6.75 (d, J=16.3 Hz, 1H, vinyl H), 6.67 (s, 1H), 6.07 (t, J=4.6 Hz, 1H, H-7'), 3.88 (s, 3H, CO₂CH₃), 2.52 (dd, J=17.0, 4.1 Hz, 1H, H-6'), 2.46 (dd, J=17.1, 5.0 Hz, 1H, H-6'), 1.48 (s, 6H, 2 x CH₃).

15 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(1-naphthalenyl)-2-naphthalenyl)-ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3300-2300 (br, s, CO₂H, aromatic, aliphatic), 1675 (s, C=O), 1600 (s, C=C).

20 ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 8.00 (d, J=8.1 Hz, 1H), 7.99 (d, J=8.2 Hz, 1H), 7.79 (d, J=8.3 Hz, 2H, H-2, H-6), 7.64-7.39 (m, 9H, naphthalenyl and H-5, H-3, H-3', H-4'), 7.04 (d, J=16.2 Hz, 1H, vinyl H), 6.91 (d, J=16.4 Hz, 1H, vinyl H), 6.53 (s, 1H, H-1'), 6.06 (t, J=4.6 Hz, 1H, H-7'), 2.46 (d, J=6.2 Hz, 2H, H-6'), 1.45 (s, 3H, CH₃), 1.43 (s, 3H, CH₃).

Anal. Calcd for C₃₁H₂₆O₂·0.5 H₂O: C, 84.71; H, 6.19.

25 Found: C, 84.93; H, 6.28.

EXAMPLE 19

30 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-isoquinolyl)-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(4-isoquinolyl)tin.

35 Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-isoquinolyl)-2-naphthalenyl)-ethenyl]benzoic acid

5

IR (KBr) ν_{\max} (cm⁻¹): 3100-2800 (w, aromatic, aliphatic), 1720 (s, C=O), 1605 (s, C=C).

¹H NMR 400 MHz (CDCl₃) δ (ppm): 9.32 (br s, 1H), 8.50 (br s, 1H), 8.07 (dd, J=6.9, 2.0 Hz, 1H), 7.91 (d, J=8.4 Hz, 2H, H-2, H-6), 7.69 (dd, J=7.2, 1.8 Hz, 1H),
10 7.64 - 7.59 (m, 2H), 7.44 (s, 2H), 7.37 (d, J=8.3 Hz, 2H, H-3, H-5), 6.89 (d, J=16.3 Hz, 1H, vinyl H), 6.75 (d, J=16.3 Hz, 1H, vinyl H), 6.65 (s, 1H), 6.15 (t, J=5.1 Hz, 1H, H-7'), 3.88 (s, 3H, CO₂CH₃), 2.57 (dd, J=17.1, 3.7 Hz, 1H, H-6'), 2.46 (dd, J=17.1, 5.4 Hz, 1H, H-6'), 1.50 (s, 3H, CH₃), 1.46 (s, 3H, CH₃).

15 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-isoquinolyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{\max} (cm⁻¹): 3700-2200 (br, s, CO₂H, HCl, aromatic, aliphatic), 1710 (s, C=O), 1600 (s, C=C).

20 ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 9.60 (s, 1H), 8.52 (s, 1H), 8.36 (d, J=7.8 Hz, 1H), 7.87 - 7.79 (m, 2H), 7.80 (d, J=8.2 Hz, 2H, H-2, H-6), 7.66 (d, J=8.2 Hz, 1H), 7.62 (d, J=8.1 Hz, 1H), 7.52 (d, J=8.4 Hz, 2H, H-3, H-5), 7.50 (m, 1H), 7.08 (d, J=16.4 Hz, 1H, vinyl H), 6.96 (d, J=16.4 Hz, 1H, vinyl H), 6.60 (s, 1H), 6.20 (t, J=4.3 Hz, 1H, H-7'), 2.49 (d, J=4.3 Hz, 2H, H-6'), 1.45 (s, 3H, CH₃),
25 1.40 (s, 3H, CH₃).

Anal. Calcd for C₃₀H₂₅NO₂·0.5 H₂O·HCl: C, 75.54; H, 5.71; N, 2.94.

Found: C, 75.74; H, 5.79; N, 2.56.

EXAMPLE 20

30

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(2-benzothiophenyl)-2-naphthalenyl)-ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(2-
35 benzothiophenyl)tin.

5

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(2-benzothiophenyl)-2-naphthalenyl)ethenyl]benzoate

¹H NMR 400 MHz (CDCl₃) δ (ppm): 7.99 (d, J=8.4 Hz, 2H, H-2, H-6), 7.87 (d, J=7.6 Hz, 1H, H-4 or H-7 in benzothiophene), 7.80 (d, J=7.6 Hz, 1H, H-4 or H-7 in benzothiophene), 7.62 (d, J=1.6 Hz, 1H, H-1'), 7.52 (d, J=8.4 Hz, 2H, H-3, H-5), 7.51 (dd, J=8.0, 1.7 Hz, 1H, H-3'), 7.41 (d, J=8.0 Hz, 1H, H-4'), 7.41-7.34 (m, 2H, H-5, H-6 in benzothiophene), 7.34 (s, 1H, H-3 in benzothiophene), 7.16 (d, J=16.3 Hz, 1H, vinyl H), 7.02 (d, J=16.3 Hz, 1H, vinyl H), 6.36 (t, J=4.8 Hz, 1H, H-7'), 3.91 (s, 3H, CO₂CH₃), 2.41 (d, J=4.8 Hz, 2H, H-6'), 1.38 (s, 6H, 2 x CH₃).

20

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(2-benzothiophenyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{max} (cm⁻¹): 3300-2200 (br, s, CO₂H, aromatic, aliphatic), 1675 (s, C=O), 1605 (s, C=C).

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 7.96 (d, J=7.8 Hz, 1H), 7.87 (m, 1H), 7.86 (d, J=8.0 Hz, 2H, H-2, H-6), 7.67 (m, 1H), 7.67 (d, J=8.3 Hz, 2H, H-3, H-5), 7.57 (s, 1H), 7.48 (s, 1H), 7.46 (d, J=8.1 Hz, 1H), 7.42 - 7.36 (m, 3H), 7.17 (d, J=16.4 Hz, 1H, vinyl H), 6.38 (t, J=4.6 Hz, 1H, H-7'), 2.36 (d, J=4.7 Hz, 2H, H-6'), 1.30 (s, 6H, 2 x CH₃).

Anal. Calcd for C₂₉H₂₄SO₂·0.5 H₂O: C, 78.17; H, 5.66.

Found: C, 78.18; H, 5.69.

30

35

5

EXAMPLE 21

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-pyrimidyl)-2-naphthalenyl)ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(5-pyrimidyl)tin.

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(5-pyrimidyl)-2-naphthalenyl)ethenyl]benzoate

¹H NMR 400 MHz (CDCl₃) δ (ppm): 9.24 (s, 1H, H-2 in pyrimidine), 8.78 (s, 2H, H-4 and H-6 in pyrimidine), 7.99 (d, J=8.3 Hz, 2H, H-2, H-6), 7.50 (d, J=8.4 Hz, 2H, H-3, H-5), 7.48 (dd, J=8.0, 1.6 Hz, 1H, H-3'), 7.42 (d, J=8.0 Hz, 1H, H-4'), 7.09 (d, J=16.3 Hz, 1H, vinyl H), 7.01 (d, J=1.5 Hz, 1H, H-1'), 6.95 (d, J=16.3 Hz, 1H, vinyl H), 6.12 (t, J=4.6 Hz, 1H, H-7'), 3.91 (s, 3H, CO₂CH₃), 2.43 (d, J=4.7 Hz, 2H, H-6'), 1.37 (s, 6H, 2 x CH₃).

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(5-pyrimidyl)-2-naphthalenyl)ethenyl]benzoic acid

IR (KBr) ν_{max} (cm⁻¹): 3300-2100 (br, s, CO₂H, aromatic, aliphatic), 1715, 1675 (s, C=O), 1605 (s, C=C).

¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 9.22 (s, 1H, H-2 in pyrimidine), 8.80 (s, 2H, H-4 and H-6 in pyrimidine), 7.87 (d, J=8.3 Hz, 2H, H-2, H-6), 7.65 (d, J=8.3 Hz, 2H, H-3, H-5), 7.63 (dd, J=8.1, 1.4 Hz, 1H, H-3'), 7.45 (d, J=8.1 Hz, 1H, H-4'), 7.34 (d, J=16.4 Hz, 1H, vinyl H), 7.15 (d, J=16.4 Hz, 1H, vinyl H), 7.05 (d, J=1.4 Hz, 1H, H-1'), 6.21 (t, J=4.6 Hz, 1H, H-7'), 2.37 (d, J=4.6 Hz, 2H, H-6'), 1.31 (s, 6H, 2 x CH₃).

Anal. Calcd for C₂₉H₂₄SO₂·0.5 H₂O: C, 78.17; H, 5.66.

Found: C, 78.18; H, 5.69.

35

5

EXAMPLE 22

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-methoxyphenyl)-2-naphthalenyl)-ethenyl]benzoic acid

- 10 The title material was prepared as described in Example 1 using tributyl(4-methoxyphenyl)tin.

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-methoxyphenyl)-2-naphthalenyl)-ethenyl]benzoate

15

- ¹H NMR 400 MHz (CDCl₃) δ (ppm): 1.36 (6H, s, 2 x -CH₃), 2.36 (2H, d, J=4.7 Hz, H-6'), 3.89 (3H, s, -OCH₃), 3.92 (3H, s, -OCH₃), 5.98 (1H, t, J=4.7 Hz, H-7'), 6.96 (1H, d, J=16.3 Hz, vinyl H), 6.94-6.98 (2H, m, H-3 and H-5 of p-MeOphenyl), 7.11 (1H, d, J=16.3 Hz, vinyl H), 7.19 (1H, d, J=1.7 Hz, H-1'), 20 7.31-7.33 (2H, m, H-2 and H-6 of p-MeOphenyl), 7.38 (1H, d, J=8.0 Hz, H-4'), 7.44 (1H, dd, J=8.0 and 1.8 Hz, H-3'), 7.49 (2H, d, J=8.4 Hz, H-3 and H-5), 7.99 (2H, d, J=8.3 Hz, H-2 and H-6).

4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-methoxyphenyl)-2-naphthalenyl)ethenyl]benzoic acid

25

- IR (nujol) ν_{\max} (cm⁻¹): 2920, 2850 (aromatic, aliphatic), 1675 (s, C=O), 1600 (s, C=C).
- ¹H NMR 400 MHz (DMSO-d₆) δ (ppm): 1.30 (6H, s, 2 x -CH₃), 2.31 (2H, d, J=4.6 Hz, H-6'), 3.81 (3H, s, -OCH₃), 5.96 (1H, d, J=4.6 Hz, H-7'), 7.00 (2H, d, J=8.7 Hz, H-3 and H-5 of p-MeOphenyl), 7.08 (1H, d, J=17.3 Hz, vinyl H), 7.10 (1H, d, H-1'), 7.27 (2H, d, J=8.8 Hz, H-2 and H-6 of p-MeOphenyl), 7.30 (1H, d, J=17.4 Hz, vinyl H), 7.42 (1H, d, J=8.1 Hz, H-4'), 7.59 (1H, dd, J=8.1 and 1.6 Hz, H-3'), 7.67 (2H, d, J=8.4 Hz, H-3 and H-5), 7.87 (2H, d, J=8.4 Hz, H-2 and H-6).
- 35

- 5 Anal. Calcd for $C_{28}H_{26}O_3$: C, 81.92; H, 6.38.
 Found: C, 81.75; H, 6.30.

EXAMPLE 23

- 10 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-benzyloxyphenyl)-2-naphthalenyl)-ethenyl]benzoic acid

The title material was prepared as described in Example 1 using tributyl(4-benzyloxyphenyl)tin.

15

Methyl 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-(4-benzyloxyphenyl)-2-naphthalenyl)-ethenyl]benzoate

- 1H NMR 400 MHz ($CDCl_3$) δ (ppm): 1.35 (6H, s, 2 x $-CH_3$), 2.36 (2H, d, $J=4.7$ Hz, H-6'), 3.92 (3H, s, $-OCH_3$), 5.15 (2H, s, $-OCH_2Ph$), 5.98 (1H, t, $J=4.6$ Hz, H-7'), 6.96 (1H, d, $J=16.3$ Hz, vinyl H), 7.05 (2H, d, $J=8.6$ Hz, H-3 and H-5 of p-OBn-phenyl), 7.11 (1H, d, $J=16.3$ Hz, vinyl H), 7.20 (1H, d, $J=1.4$ Hz, H-1'), 7.32 (2H, H-2 and H-6 of p-OBn-phenyl), 7.36-7.45 and 7.49-7.52 (9H, 2 sets of m, H-3, H-5, H-3', H-4', phenyl), 7.99 (2H, d, $J=8.3$ Hz, H-2 and H-6).
- 20

- 25 4-[(E)-(5,6-Dihydro-5,5-dimethyl-8-(4-benzyloxyphenyl)-2-naphthalenyl)-ethenyl]benzoic acid

IR (nujol) ν_{max} (cm^{-1}): 2950, 2850 (aromatic, aliphatic), 1675 (C=O), 1605 (C=C).

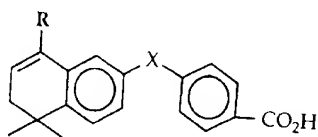
- 1H NMR 400 MHz ($DMSO-d_6$) δ (ppm): 1.30 (6H, s, 2 x $-CH_3$), 2.31 (2H, d, $J=4.4$ Hz, H-6'), 5.16 (2H, s, $-OCH_2Ph$), 5.97 (1H, t, $J=4.5$ Hz, H-7'), 7.06-7.51 (13H, 5 sets of m, H-1', H-4', vinyl H, H-2, H-3, H-5, H-6 of BnOphenyl, phenyl), 7.60 (1H, br d, $J=7.8$ Hz, H-3'), 7.67 (2H, d, $J=8.2$ Hz, H-3 and H-5), 7.88 (2H, d, $J=8.3$ Hz, H-2 and H-6).
- 30

Anal. Calcd for $C_{34}H_{30}O_3$: C, 83.92; H, 6.21.

- 35 Found: C, 84.00; H, 5.80.

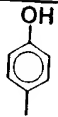
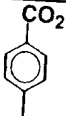
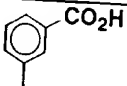
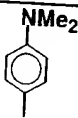
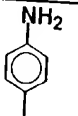
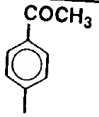
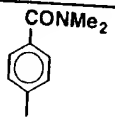
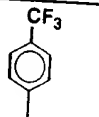
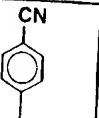
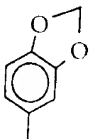
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
Following the general procedures of Examples 1-23 above, the following additional compounds were prepared (X = -CH=CH-).



10

Ex. No.	R	Mol. Form.	Microanalysis			
				C	H	N
24		C ₂₅ H ₂₂ O ₂ S	Calc'd. Found:	77.69 77.53	5.74 5.74	
25		C ₂₅ H ₂₂ O ₃	Calc'd. Found:	81.06 82.01	5.99 6.04	
26		C ₃₀ H ₂₅ NO ₂ .HCl	Calc'd. Found:	76.99 76.65	5.60 5.99	2.99 2.88
27	H	C ₂₁ H ₂₀ O ₂	Calc'd. Found:	82.87 82.71	6.62 6.21	
28		C ₂₈ H ₂₆ O ₃	Calc'd. Found:	81.92 81.70	6.38 5.98	
29		C ₂₇ H ₂₄ O ₃ 0.3 H ₂ O 0.05 CH ₃ CN	Calc'd. Found:	80.58 80.47	6.18 6.41	

30		$C_{27}H_{24}O_3$ 0.1 H_2O 0.1 CH_3CN	Calc'd. Found:	81.19 81.16	6.14 6.04	
31		$C_{28}H_{24}O_4$ 0.1 H_2O 0.05 THF	Calc'd. Found:	78.79 78.62	5.77 5.23	
32		$C_{28}H_{24}O_4$ 0.5 H_2O 0.05 THF	Calc'd. Found:	77.49 77.36	5.86 5.84	
33		$C_{29}H_{29}NO_2$ 0.2 THF	Calc'd. Found:	81.72 81.53	7.04 7.06	3.20 3.14
34		$C_{27}H_{25}NO_2$	Calc'd. Found:	81.99 81.51	6.37 5.87	
35		$C_{29}H_{26}O_3$ 0.2 THF 0.05 CH_3CN	Calc'd. Found:	81.80 81.58	6.37 6.25	
36		$C_{30}H_{29}NO_3$	Calc'd. Found:	79.79 80.34	6.47 6.45	3.10 3.05
37		$C_{28}H_{23}F_3O_2$	Calc'd. Found:	74.98 74.81	5.17 5.13	
38		$C_{28}H_{23}NO_2$ 0.1 H_2O 0.1 THF	Calc'd. Found:	82.29 82.17	5.84 5.27	3.38 3.07
39		$C_{28}H_{24}O_4$ 0.1 CH_3CN	Calc'd. Found:	79.02 79.02	5.72 5.49	

40		C ₂₇ H ₂₅ NO ₂ 0.5 H ₂ O 0.3 CH ₃ CN	Calc'd. Found:	79.53 79.37	6.51 5.81	4.37 4.39
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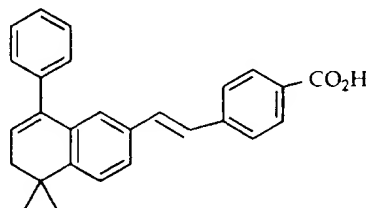
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Biological ActivityPrevention of Surgical Adhesions

10

Models of peritoneal adhesions induced by surgical trauma have been used to predict the clinical activity of a number of marketed anti-adhesion barrier devices. One such model is the trauma-induced caecal adhesion model in rats. A representative retinoid antagonist compound of the present invention, 4-[(E)-(5,6-dihydro-5,5-dimethyl-8-phenyl)-2-naphthalenyl]vinyl]benzoic acid of the formula

15



[referred to below as compound A] was used with this model to demonstrate efficacy.

20

Adult female Wistar rats were used in our studies. The trauma induction was carried out using aseptic conditions in animals anesthetized with a mixture of Ketamine (100 mg/kg) and Rompun (10 mg/kg) given IP. A 2 cm midline abdominal incision was made and the

5 caecum was exteriorized. Both sides of the caecum were abraded with a
dry gauze until there was evidence of punctate bleeding. After replacing
the organ in the abdominal cavity, the incision was closed. Trauma to the
caecum produces fibrous scar tissue or adhesions to adjacent organs,
peritoneal wall, or the omentum. Animals were treated with test
10 compound orally or by intravenous injection or intra-abdominally by
direct instillation into the peritoneal cavity. Oral treatments were
administered once daily for up to 7 days. Intra-abdominal treatments
were applied once post-trauma and just prior to wound closure.

15 On the seventh postoperative day, the animals were sacrificed and
the peritoneal cavity was exposed and examined for adhesions. Three
criteria that were used to evaluate the adhesions are: severity of the
adhesions, extent or area of the caecum involved with adhesions and the
number of adhesions formed in each animal. Statistical analysis of the
20 data was performed using students' T test. The following scoring system
was used:

<u>Grade</u>		<u>Description</u>
0	=	no adhesions;
25 1.0	=	easily separable, filmy, non-vascularized adhesions covering 25% of the caecum;
2.0	=	dense adhesions separated by blunt dissection and involving 50% of the caecum;

5	3.0	=	dense, fibrous, vascularized adhesions requiring sharp dissection and covering 75% of the caecum;
	4.0	=	severe, dense, vascularized adhesions unable to separate without tearing the adjacent
10			membranes and covering greater than 75% of the caecum.

The test compound administered orally for 7 days had a significant dose-dependent effect on the number and severity of adhesions formed.

15 FIG. 1 shows that compared to the vehicle control, the test compound A significantly reduced the number and severity of adhesions per animal at 10 and 15 mg/kg.

A comparison of all-trans retinoic acid (RA) and representative
20 retinoid antagonist compounds of the present invention on the number of, severity and extent of caecal adhesions is shown in table I. All-trans retinoic acid, the triple agonist, tested at twice the dose of the above-described test compound demonstrated no significant effect on trauma induced adhesions. In contrast, retinoid antagonists Compound B and
25 Compound D dose-dependently reduced adhesion number and severity.

Table 1**(Comparison of Orally Administered Retinoid Antagonists Compound****B & D to All Trans Retinoic Acid)**

Treatment	Dose (mg/kg)	Mean # of Adhesions per Rat +/- SEM	Mean Adhesion Severity Grade per Rat +/- SEM
Vehicle Control		3.8 +/- 0.8	8.0 +/- 1.7
Compound B	0.5	3.8 +/- 0.7	7.4 +/- 1.7
Compound B	5.0	1.8 +/- 0.6	3.6 +/- 1.5
Compound B	10.0	1.2* +/- 0.7*	1.8* +/- 1.3*
Vehicle Control		7.6 +/- 0.9	21.2 +/- 2.8
Compound D	1.0	6.0 +/- 0.8	14.2 +/- 2.7
Compound D	3.0	2.8 +/- 0.8*	6.0 +/- 1.6*
Compound D	10.0	2.2 +/- 0.6*	4.6 +/- 1.0*
Compound D	15.0	2.4 +/- 0.7*	5.0 +/- 1.5*
Vehicle Control		7.5 +/- 0.6	16.25 +/- 1.7
All Trans Retinoic Acid	1.0	7.8 +/- 0.9	20.2 +/- 2.0
All Trans Retinoic Acid	10.0	5.6 +/- 0.8	13.8 +/- 2.5
All Trans Retinoic Acid	30.0	6.6 +/- 0.9	16.8 +/- 2.2

*p = 0.005

The test compound described above administered by the intra-abdominal route was compared to some other representative retinoid

5 antagonists of the present invention. A single dose of compound in 3 ml
volume was instilled over the traumatized caecum and abdominal cavity
prior to closing the incision. Seven days later the animals were sacrificed
and the abdominal cavity was examined for adhesions to the caecum.
Compared to the vehicle control, a single intra-abdominal application of
10 compound A at 5 mg significantly reduced the number of adhesions
formed. At this dose compound A also effectively reduced the severity of
caecal adhesions as illustrated by the results in table 2. Each of the other
compounds tested also showed significant reduction in the number and
severity of adhesions formed.

15

Table 2

**(Effect of Retinoid Antagonist Compounds following a single intra-
abdominal treatment in the trauma-induced caecal adhesion in rats)**

Treatment	Dose (mg/kg)	Mean # of Adhesions per Rat +/- SEM	Mean Adhesion Severity Grade per Rat +/- SEM
Vehicle Control		6.6 +/- 0.8	8.4 +/- 1.1
Compound A	0.5	6.4 +/- 0.9	8.4 +/- 1.5
Compound A	2.0	4.2 +/- 1.3	5.6 +/- 2.2
Compound A	5.0	2.3 +/- 0.75*	2.3 +/- 0.75*
Vehicle Control		6.4 +/- 0.2	13 +/- 0.4

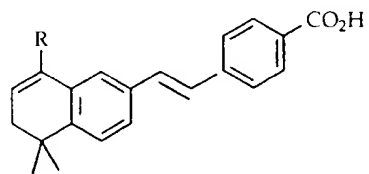
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Compound B	0.5	5.8 +/- 1.4	11.2 +/- 3.2
Compound B	1.5	2.2 +/- 0.5*	4.2 +/- 1*
Compound B	5.0	2.4 +/- 0.8*	4.8 +/- 1.9*
Vehicle Control		7.8 +/- 0.5	18.4 +/- 0.8
Compound C	0.3	6.3 +/- 0.3	21.3 +/- 2.3
Compound C	1.0	5.5 +/- 0.9	13 +/- 2.1*
Compound C	3.0	5.8 +/- 0.8	14.2 +/- 0.11*
Vehicle Control		6.0 +/- 0.8	16.6 +/- 1.6
Compound D	0.3	6.2 +/- 0.7	13.4 +/- 1.7
Compound D	1.0	3.2 +/- 0.6*	6.4 +/- 1.3*
Compound D	3.0	2.0 +/- 0.3*	3.6 +/- 0.8*
Vehicle Control		8.0 +/- 1.9	18.8 +/- 1.9
Compound E	0.3	6.5 +/- 0.6	20.3 +/- 1.3
Compound E	1.0	7.5 +/- 0.3	20 +/- 1.1*
Compound E	3.0	4.40 +/- 1.1*	9.6 +/- 2.4*

5

*p = 0.01

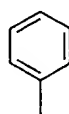
5 Structures of test compounds:



Compound A

R

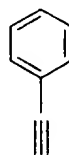
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10 Compound B

R

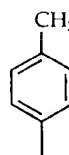
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Compound C

R

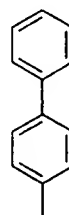
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Compound D

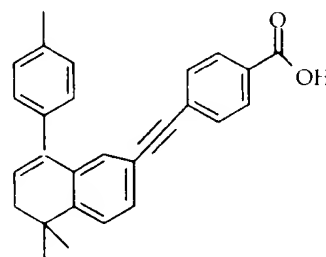
R

=



Compound E

=



5

As shown above the compounds of the present invention are useful in the prevention of post-surgical adhesions.

For prevention of surgical adhesions, the retinoid antagonist may
10 be administered by a variety of systemic and local methods. The compounds may be administered orally, by intravenous injection, by intramuscular injection or by intracavity instillation. The general range of doses will depend on the efficacy of each compound and the intended route but is expected to be from 0.1 mg/kg to 100 mg/kg with a preferred
15 range of 1 to 25 mg/kg. Preferred routes of administration are oral administration or direct administration (intracavity instillation) to a site of surgical activity on an organ surface.

The term of administration may vary depending upon a number of
20 factors which would be readily appreciated by those skilled in the art. In general, administration of a retinoid antagonist of the present invention should be effected 12-48 hours prior to the time of surgery and for at least 24-48 hours post-surgery. In general the retinoid antagonist may be administered from 72 hours prior to surgery and continue up to 2 weeks
25 after surgery and preferably for a period 12 hours prior to surgery and continuing 48 hours after surgery.

5 For intracavity administration the retinoid can be administered in a suitable vehicle such as 5% dextrose in water adjusted to a pH to assure complete salt formation. However it is understood that many other single dose delivery systems could be contemplated by those skilled in the art including microcapsules, microspheres, liposomes, viscous instillates,
10 and polymeric delivery materials.

 The retinoid antagonists of formula II above may be used topically or systemically, as anticancer agents and in the treatment, amelioration or prevention of the skin disorders and rheumatic illnesses (including
15 rheumatoid arthritis) described in EP 661,259 A1 and in U.S. Patent 5,618,839. In this regard they may be used for therapy in animals, including humans, of premalignant epithelial cell lesions, as a prophylaxis against tumor promotion in epithelial cells and treatment for dermatoses such as ichthyoses, follicular disorders, benign epithelial
20 disorders and other proliferative skin diseases such as acne, psoriasis, eczema, atopic dermatitis, non-specific dermatosis and the like. They may also be used in reversing and preventing the effects of irradiation damage to skin. When used for the above purposes, they will usually be formulated with a pharmaceutically acceptable liquid, semi-solid, or solid
25 carrier. A pharmaceutically acceptable carrier is a material that is nontoxic and generally inert and does not affect the functionality of the active ingredients adversely. Such materials are well known and include those materials sometimes referred to as diluents or vehicles (excipients) in the

5 pharmaceutical formulation art. The carrier may be organic or inorganic
in nature. Examples of pharmaceutically acceptable carriers that may be
used to formulate a compound of formula I are water, gelatin, lactose,
starch, mineral oil, cocoa butter, dextrose, sucrose, orbital, mannitol, gum
acacia, alginates, cellulose, talc, magnesium stearate, polyoxyethylene
10 sorbitan monolaurate, and other commonly used pharmaceutical carries.
In addition to a compound of formula I and carrier, the formulation may
contain minor amounts of additives such as flavoring agents, coloring
agents, thickening or gelling agents, emulsifiers, wetting agents, buffers,
stabilizers, and preservatives such as antioxidants.

15

The dosages and dosage regimen in which the compounds of
formula I are administered will vary according to the dosage form, mode
of administration, the condition being treated and particulars of the
patient being treated. Accordingly, optimal therapeutic concentrations
20 will be best determined at the time and place through routine
experimentation.

In the treatment of dermatoses, it will generally be preferred to
administer the drug topically, though in certain cases such as treatment of
25 severe cystic acne, oral administration may also be used. If the
compounds according to the invention are used topically, it will be found
that they exhibit a good activity over a very broad range of dilution; in
particular, concentrations of the active compound or compounds ranging

5 from 0.0005% to 2% by weight can generally be used. It is of course possible to use higher concentrations if this should become necessary for a particular application; however, the preferred concentration of active principle are from 0.002% to 1% by weight.

10 For topical administration the compounds of formula I are conveniently provided in the form of unguents, gels, creams, ointments, powders, dyeing compositions, solutions, suspension, emulsions, lotions, sprays, adhesive plasters and impregnated pads. The compounds according to the invention can be mixed with inert nontoxic, generally
15 liquid or pasty, bases suitable for topical treatment. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. Other medicaments can be added to such formulation for such secondary
20 purposes as treating skin dryness, providing protection against light; other medications for treating dermatoses, preventing infection, reducing irritation, inflammation and the like.

The compounds according to the invention can also be used
25 enterally. Orally, the compounds according to the invention are suitable administered at the rate of 100 μ g to 100 mg per day per kg of body weight. The required dose can be administered in one or more portions. For oral administration, suitable forms are, for example, tablets, pills, dragees,

5 syrops, suspensions, emulsions, solutions, powders and granules; a preferred method of administration consists in using pills containing from 1 mg to about 25 mg of active substance.

U.S. Patent No. 4,876,381 issued on October 24, 1989 to Lang et al.

10 provides examples of formulations constituting gel, unguent, powder, cream, etc. for a retinoid compound. The aforesaid U.S. patent can be used as a guide to formulate a compound of formula I and is herein incorporated by reference in its entirety.

15 Isotretinoin (Accutane®) and etretinate (Tegison®) are used clinically to treat severe recalcitrant cystic acne and severe recalcitrant psoriasis, including the erythrodermica and generalized pustular types, respectively. Their mode of use is amply illustrated in the Physicians's Desk Reference, 47th Edition, 1993, published by Medical Economics Data.

20 The compounds of formula II may also be used to treat severe recalcitrant cystic acne or severe recalcitrant psoriasis. In so doing, the compounds of the present invention may be used in a similar fashion to isotretinoin and etretinate; thus, the relevant sections on isotretinoin and etretinate in the Physician's Desk Reference will serve as a convenient guide which will

25 obviate the need for any undue experimentation.

The compounds according to the invention can also be administered parenterally in the form of solutions or suspensions for

5 intravenous or intramuscular perfusions or injections. In that case, the compounds according to the invention are generally administered at the rate of about 10 µg to 10 mg per day per kg of body weight; a preferred method of administration consists of using solutions or suspensions containing approximately from 0.01 mg to 1 mg of active substance per ml.

10

Several retinoids have been found to possess anti-tumor properties. Roberts, A.B. and Sporn, M.B. in "The Retinoids", Sporn, M.B., Roberts, A.B., and Goodman, D.S., eds, 1984, 2 pp. 209-286, Academic Press, New York; Lippman, S.M., Kessler, J.F., and Meyskens, F.L., Cancer Treat. Rep., 15 1987, 71, p. 391; *ibid.*, p. 493. As used herein, the term "anti-tumor" includes both chemopreventative (prophylactic or tumor promotion inhibiting) and therapeutic (curative) use. For example, all-trans retinoic acid can be used to treat acute promyelocytic leukemia. Huang, M. Et al., Blood, 1988, 72, p. 567. Isotretinoin has been shown to be useful in 20 prevention of second primary tumors in squamous-cell carcinoma of the head and neck. Hong, W.K. et al., N. Engl. J. Med., 1990, 323, p. 795.

The compounds of formula II can also be used in substantially the similar manner to retinoids for treating (both chemopreventively and 25 therapeutically) various tumors. For the compounds of this invention, the anti-tumor dose to be administered, whether a single dose, multiple dose, or a daily dose, will of course vary with the particular compound employed because of the varying potency of the compound, the chosen

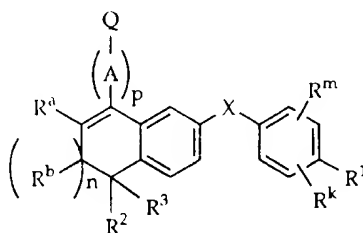
5 route of administration, the size of the recipient, the type of tumor, and
the nature of the patient's condition. The dosage to be administered is not
subject to definite bounds, but it will usually be an effective amount, or
the equivalent on a molar basis of the pharmacologically active free form
produced from a dosage formulation upon the metabolic release of the
10 active drug to achieve its desired pharmacological and physiological
effects. An oncologist skilled in the art of cancer treatment will be able to
ascertain, without undue experimentation, appropriate protocols for the
effective administration of the compounds of this present invention, such
as by referring to the earlier published studies on retinoids found to have
15 anti-tumor properties. For example, for the prevention of second primary
tumors with a compound of formula II in squamous-cell carcinoma of the
head and neck, an oncologist may refer to the study by Hong, W.K. et al. in
N. Engl. J. Med., 1990, 323, p. 795. For treating acute promyelocytic
leukemia, the oncologist may refer to the study by Huang, M. et al. in
20 Blood, 1988, 72, p. 567.

5

CLAIMS

We claim:

- 10 1. A retinoid antagonist compound having the formula



II

- or nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable
 15 esters or solvates thereof, in which

- X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-,
 20 -NHCH₂- or -CR⁵ = CR⁶-;
 R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆ alkyloxy or nitro;
 n is zero or one;

-106-

- 5 A is $-\text{NH}(\text{CH}_2)_m-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{O}-$, $-\text{C}\equiv\text{C}-$, $-\text{CR}^8\text{R}^9$,
 $-\text{CR}^8 = \text{CR}^9-$, phenyl, phenyl substituted by a C_{1-6} alkyl,
 C_{1-6} alkoxy, halogen, CO_2R^8 , $-(\text{CH}_2)_m\text{OR}^8$, $-(\text{CH}_2)_m\text{NR}^9\text{R}^8$,
or $-\text{COR}^{10}$ group, naphthyl, naphthyl substituted by a
 C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CO_2R^8 , $-(\text{CH}_2)_m\text{OR}^8$,
10 $-(\text{CH}_2)_m\text{NR}^8\text{R}^9$ or $-\text{COR}^{10}$, or heteroaryl;
Q is phenyl, naphthyl or heteroaryl, said phenyl, naphthyl
or heteroaryl group being optionally substituted by one
to three same or different C_{1-6} alkyl, C_{1-6} fluoroalkyl,
 C_{1-6} alkoxy, halogen, CO_2R^{11} , $-(\text{CH}_2)_q\text{OR}^{11}$,
15 $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or $-\text{COR}^{13}$ with the proviso
that when A is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{O}-$, then Q is a
phenyl, naphthyl or heteroaryl group substituted by
one to three halogen, C_{1-6} fluoroalkyl, CO_2R^{11} ,
 $-(\text{CH}_2)_q\text{OR}^{11}$, $-(\text{CH}_2)_q\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{13}$ or $-\text{COR}^{13}$;
20

R^5 and R^6 are each independently hydrogen or C_{1-6} alkyl;

R^8 and R^9 are each independently hydrogen or C_{1-6} alkyl;

- 25 R^{10} and R^{13} are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;

R^{11} and R^{12} are each independently hydrogen or C_{1-6} alkyl;

-107-

- 5 R^a and R^b are independently hydrogen or C_{1-6} alkyl; but when n is one, R^a and R^b together can form a radical of the formula



- 10 Z is hydrogen, C_{1-6} alkyl, benzyl, *p*-methoxybenzyl, allyl or trimethylsilylethyl;

m and q are independently 0 to 2;

- 15 p is 0 or 1 with the proviso that when p is 0 then Q is phenyl, naphthyl or heteroaryl substituted by one to three $-(CH_2)_qOR^{11}$, $-(CH_2)_qNR^{11}R^{12}$, or $-COR^{13}$;

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

20

R^1 is $-CO_2Z$, C_{1-6} alkyl, $-CH_2OH$, $-CONHR^7$ or CHO ;

R^7 is hydrogen or C_{1-6} alkyl;

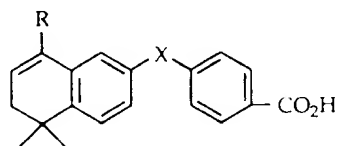
provided that when X is $-C\equiv C-$, A is not $-CR^8 = CR^9-$ or $-C\equiv C-$.

25

2. A retinoid antagonist compound having the formula

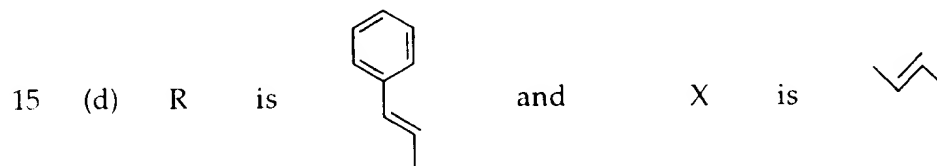
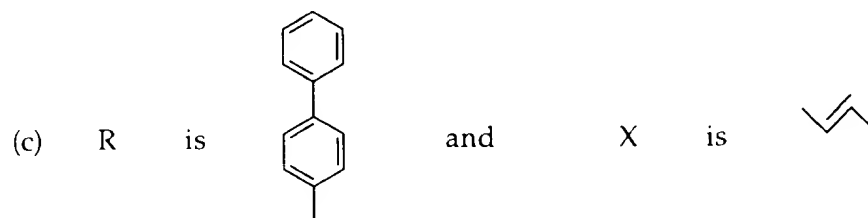
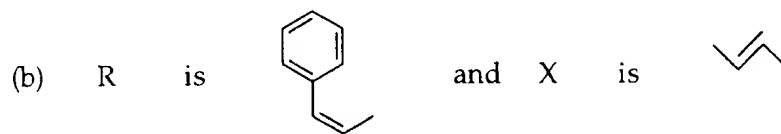
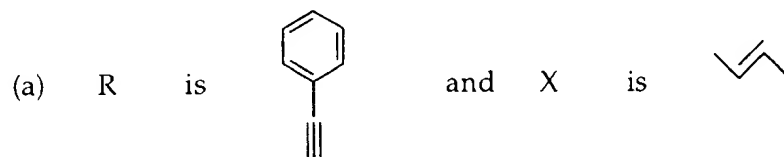
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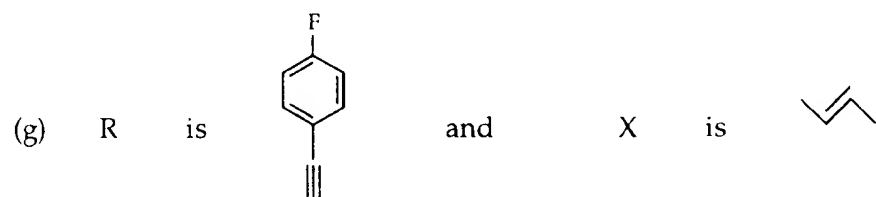
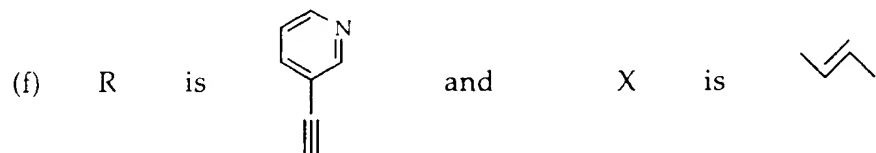
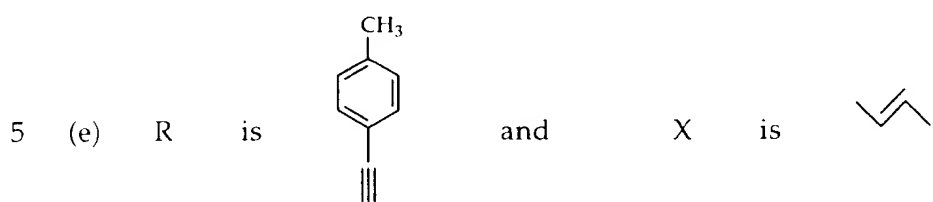
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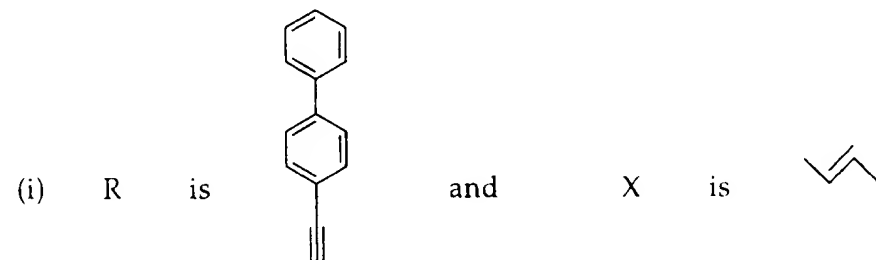
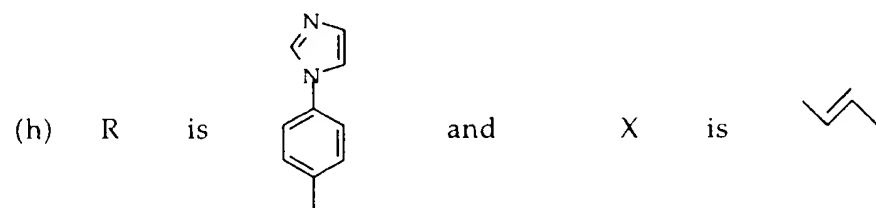
wherein

10

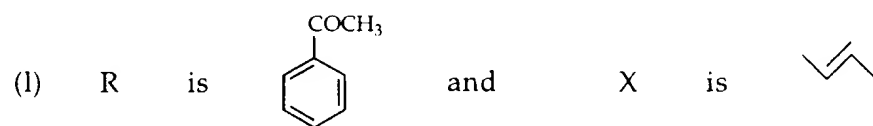
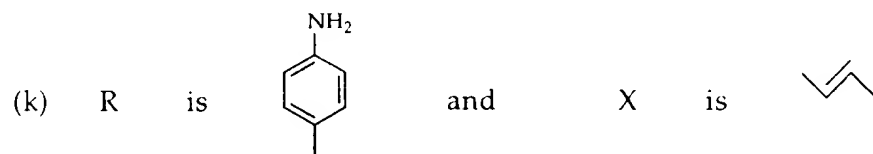
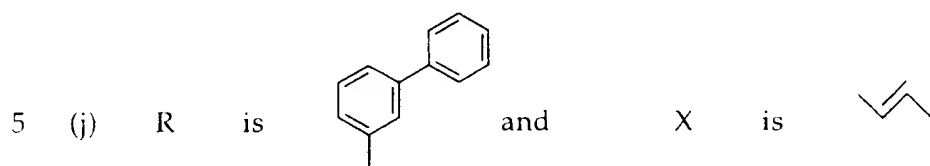




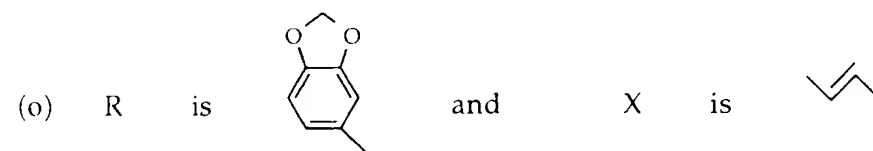
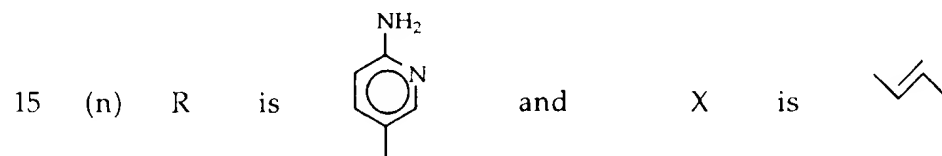
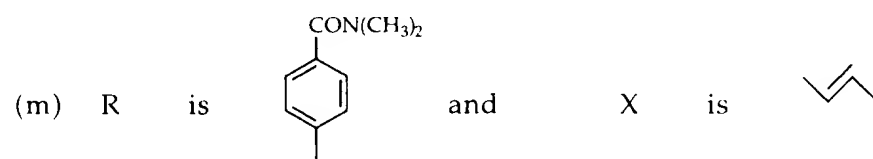
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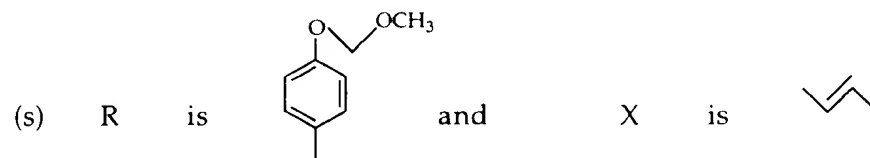
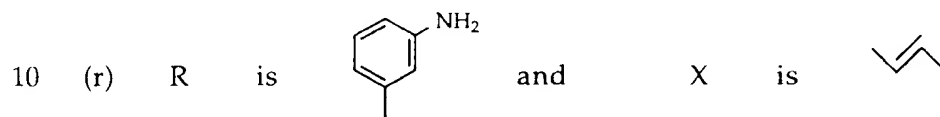
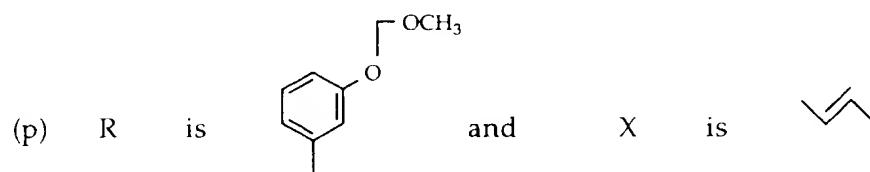
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10



5



- 15 3. A method for treating in a host mammal, one or more of the diseases and conditions selected from the group consisting of chronic skin inflammatory diseases, rheumatic diseases, non-malignant proliferative skin conditions and malignant tumors, which comprises administering to
- 20 said host an effective therapeutic amount of a compound of Claim 1 or a pharmaceutical composition thereof.

-112-

5 4. A method for the minimization or prevention of post-surgical
adhesion formation between organ surfaces comprising administering to
an animal host an effective amount of a retinoic acid antagonist for a
period of time sufficient to permit tissue repair.

10 5. The method of Claim 4 wherein the retinoid antagonist is a
compound of Claim 1.

6. The method of Claim 4 wherein the retinoid antagonist is a
compound of Claim 2.

15

7. The method of Claim 4 wherein the retinoid antagonist is
administered orally.

8. The method of Claim 4 wherein the retinoid antagonist is
20 administered directly to a site of surgical activity on an organ surface.

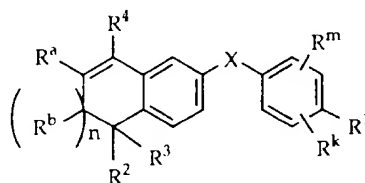
9. A pharmaceutical composition comprising a therapeutically
effective amount of a compound of claim 1 and a pharmaceutically
acceptable carrier or excipient.

25

10. A method for the minimization or prevention of post-surgical
adhesion formation between organ surfaces comprising administering to
an animal host an effective amount of a retinoic acid antagonist for a

-113-

- 5 period of time sufficient to permit tissue repair, said retinoic acid antagonist having the formula



IA

- 10 or a nontoxic pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof, in which

- X is -O-CO-, -NH-CO-, -CS-NH-, -CO-O-, -CO-NH-, -COS-,
 -SCO-, -SCH₂-, -CH₂-CH₂-, -C≡C-, -CH₂-NH-,
 15 -COCH₂-, -NHCS-, -CH₂S-, -CH₂O-, -OCH₂-, -NHCH₂- or
 -CR⁵ = CR⁶;
- R^m and R^k are independently hydrogen, halogen, C₁₋₆ alkyl, hydroxy,
 C₁₋₆alkyloxy or nitro;
- n is zero or one;
- 20 R⁴ is -(CH₂)_t-Y;
- R¹ is -CO₂Z, -C₁₋₆ alkyl, CH₂OH, -CONHR^y or CHO;
- R² and R³ are independently hydrogen or C₁₋₆ alkyl;
- R^a and R^b are independently hydrogen or C₁₋₆ alkyl; but when n is
 25 one, R^a and R^b together can form a radical of the
 formula

-114-



5

Y is phenyl or naphthyl and both radicals can be optionally substituted with one to three same or different C_{1-6} alkyl or halogen groups;

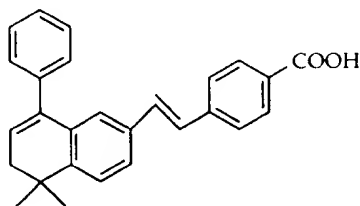
Z is hydrogen or C_{1-6} alkyl;

10 R^5 , R^6 and R^7 are independently hydrogen or C_{1-6} alkyl; and

t is zero to six.

11. The method of Claim 10 wherein the retinoid antagonist is the compound having the formula

15



12. The method of Claim 10 or Claim 11 wherein the retinoid antagonist is administered orally.

20

13. The method of Claim 10 or Claim 11 wherein the retinoid antagonist is administered directly to a site of surgical activity on an organ surface.

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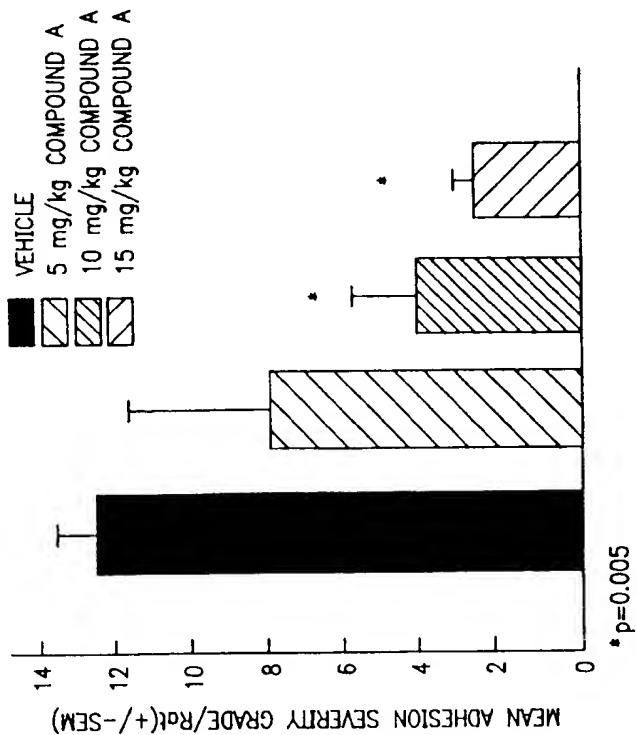


FIG. 1B

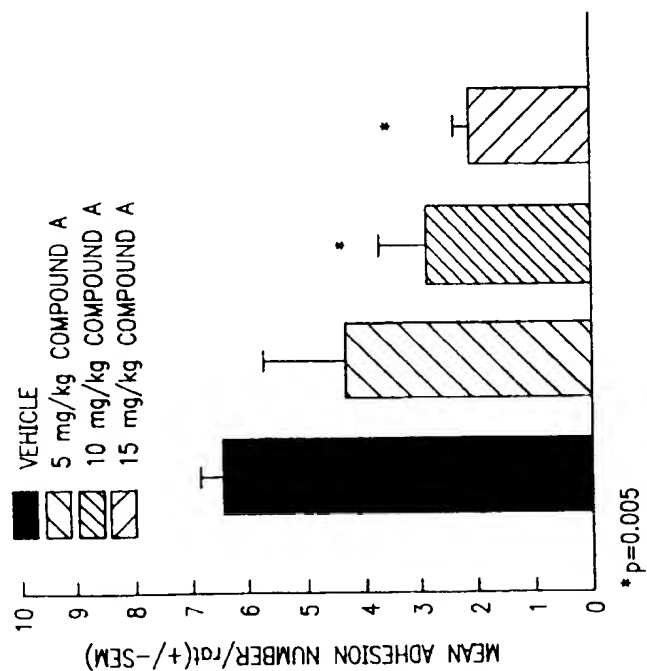


FIG. 1A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06930

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/445, 31/415, 31/38, 31/34, 31/27

US CL : 514/481, 315, 401, 438, 461, 825, 886

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/481, 315, 401, 438, 461, 825, 886

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
noneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Cas-online, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,876,381 A (LANG et al.) 24 October 1989, see the entire document.	1-13
X	WO 97/09297 A2 (ALLERGAN) 13 March 1997, see the entire document.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* E* earlier document published on or after the international filing date	* Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A* document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means	
* P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

18 JUNE 1998

Date of mailing of the international search report

20 JUL 1998

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